In the United States Court of Federal Claims

OFFICE OF SPECIAL MASTERS

Filed: July 5, 2018

KATIE SMITH,	*	
	*	
Petitioner,	*	No. 14-848V
	*	Special Master Sanders
v.	*	
	*	Entitlement Hearing; Denial of Entitlement;
SECRETARY OF HEALTH	*	Hepatitis B ("Hep B") Vaccine; Transverse
AND HUMAN SERVICES,	*	Myelitis ("TM"); *Althen* Causation; *Althen*
	*	Prong One; *Althen* Prong Two; *Althen* Prong
Respondent.	*	Three

Diana L. Stadelnikas, Maglio, Christopher and Toale, PA, Sarasota, FL, for Petitioner.
Darryl R. Wishard, United States Department of Justice, Washington, DC, for Respondent.

DECISION ON ENTITLEMENT[1]

On September 12, 2014, Katie Smith ("Petitioner") filed a petition pursuant to the National Vaccine Injury Compensation Program.[2] Petitioner alleged that the Hepatitis B ("Hep B") vaccine that she received on April 18, 2013 caused her to develop Transverse Myelitis ("TM").

After carefully analyzing and weighing all of the evidence and testimony presented in this case in accordance with the applicable legal standards, the undersigned finds that Petitioner has not met her legal burden. Petitioner has failed to provide preponderant evidence that the Hep B vaccination Petitioner received on April 18, 2013 caused her to develop TM. Accordingly, Petitioner is not entitled to compensation.

[1] This decision shall be posted on the United States Court of Federal Claims' website, in accordance with the E-Government Act of 2002, 44 U.S.C. § 3501 note (2012) (Federal Management and Promotion of Electronic Government Services). In accordance with Vaccine Rule 18(b), a party has 14 days to identify and move to delete medical or other information that satisfies the criteria in § 300aa-12(d)(4)(B). Further, consistent with the rule requirement, a motion for redaction must include a proposed redacted decision. If, upon review, the undersigned agrees that the identified material fits within the requirements of that provision, such material will be deleted from public access.

[2] The Program comprises Part 2 of the National Childhood Vaccine Injury Act of 1986, 42 U.S.C. §§ 300aa-10 et seq. (hereinafter "Vaccine Act," "the Act," or "the Program").

I. Procedural History

This case was originally assigned to Special Master Hamilton-Fieldman. *See* ECF No. 4. Petitioner filed sixteen medical records on September 19, 2014[3] and one additional medical record on October 14, 2014. *See* Notice of Filing Pet'r Exs. 1-16 on CD, ECF No. 5; Pet'r Ex. 17, ECF No. 12. After subpoenas were authorized, Petitioner submitted ten additional exhibits. *See* Notice of Filing Pet'r Exs. 18-20 on CD, ECF No. 14; Pet'r Exs. 21-26, ECF No. 17; Pet'r Ex. 27, ECF No. 18. She filed a statement of completion on December 29, 2014. ECF No. 19. Petitioner then filed an expert report on August 14, 2015. Pet'r Ex. 28, ECF No. 34.

Respondent filed a Rule 4(c) Report on February 8, 2016. ECF No. 44. In his Report, Respondent agreed with the diagnosis of TM and agreed that Petitioner suffered from residual effects or complications of TM for more than six months. *Id.* at 8. However, Respondent argued that compensation is not appropriate in this case, because Petitioner did not provide a "reliable, persuasive, explanation or theory as to how the Hep B vaccine can play a role in causing TM in general, or how it did so based on the specific facts of her case." *Id.* at 8. Respondent further opined that the length of time between the vaccination and Petitioner's onset of symptoms "is too long for the Hep B vaccine to have caused [P]etitioner's TM based on [Petitioner's expert's] theory of molecular mimicry." *Id.* at 9. In support of his position, Respondent filed an expert report on the same day as his Rule 4(c) Report. Resp't Ex. A, ECF No. 44-1.

Petitioner then filed seven additional medical records and a supplemental expert report. Pet'r Exs. 43-48, ECF No. 46; Pet'r Ex. 49, ECF No. 49; Pet'r Ex. 50, ECF No. 51. At a status conference held on August 15, 2016, Petitioner sought to schedule an entitlement hearing, but Special Master Hamilton-Fieldman and Respondent's counsel questioned the efficacy of a hearing in this case. Scheduling Order, ECF No. 53. Petitioner's counsel requested the opportunity for Petitioner to be heard at an entitlement hearing, and later elaborated that a hearing would be necessary to expand upon Petitioner's expert's opinions and to provide the opportunity to cross-examine Respondent's expert. *Id.*; Pet'r Status Report, ECF No. 55.

The case was reassigned to the undersigned on January 10, 2017. *See* ECF Nos. 56, 57. An entitlement hearing was set for December 8, 2017. Hearing Order, ECF No. 60. Petitioner filed three additional medical records before the hearing. Pet'r Exs. 62-64, ECF No. 69. The hearing was held on December 8, 2017.

[3] The CD filed on September 19, 2014, which contained Petitioner's Exhibits 1-16, was stricken from the record due to missing page numbers on two of the exhibits. See Ord. Striking CD, ECF No. 72. However, all of the exhibits were later re-filed. *See* Notice of Intent to File on CD, ECF No. 73; Unnumbered Entry (Dec. 4, 2017).

II. Factual Background

A. Medical Records

Petitioner filed thirty-seven medical records. Pet'r Exs. 1-27, 43-49, 62-64. The medical records from prior to Petitioner's Hepatitis B vaccinations reflect that she was a female in her early twenties, with the majority of her medical visits relating to a pregnancy or intermittent low back pain. Petitioner's records also reflect that her back pain worsened after she received an epidural during childbirth. *See, e.g.*, Pet'r Exs. 7 at 204-235, 14 at 7-8, 23 at 182; *see generally* Pet'r Ex. 13. Petitioner smoked and reported occasional alcohol use to some providers. Pet'r Ex. 13 at 180; Pet'r Ex. 14 at 7. A report from the North Okaloosa Medical Center dated February 28, 2012 reflects that Petitioner had presented to that emergency department twenty-one times in the prior eight years. Pet'r Ex. 7 at 203. Six of those visits were detailed on that report and reflect that Petitioner was seen for an allergic reaction, back pain, a rash, cystitis, dysmenorrhea, and a post-cesarean wound infection. *Id.*

Petitioner received the first Hep B vaccine of the series at issue here on October 15, 2012. Pet'r Ex. 15 at 1-2. She received the second on November 16, 2012, and the third on April 18, 2013. *Id.* at 1; Pet'r Ex. 48 at 3. The only medical visit documented between the first and third vaccination was a visit to a hospital on February 8, 2013 for ear and eye problems. Pet'r Ex. 11 at 105-130. She was diagnosed with otitis media and bacterial conjunctivitis on that date. *Id.*

On June 24, 2013, sixty-seven days after her third Hep B vaccine was administered on April 18, 2013, Petitioner reported to Twin Cities Hospital with complaints of shortness of breath, abdominal pain, and numbness on the right side of her body. Pet'r Ex. 11 at 74. Dr. Louis Vagias, an emergency room physician, documented that Petitioner complained of sudden-onset abdominal pain which radiated to the middle of her back. *Id.* at 39. She also complained of decreased sensation, which started with right lower numbness and difficulty walking and then progressed to "bilateral[] numbness." *Id.*

Dr. Vagias obtained a neurology tele-medicine consult from Dr. Mitch Rubin. Pet'r Ex. 11 at 52-56. Dr. Vagias reported that a workup for possible abdominal causes was negative. *Id.* at 53. Although abdominal pain had resolved, Petitioner's lower extremity numbness persisted from approximately T6 downward, and she had developed bilateral lower extremity weakness. *Id.* Dr. Rubin reported that acute thoracic disc, TM, and aortic dissection were possible considerations, and recommended that the hospital obtain an MRI of the thoracic and cervical spine, as well as a CTA of the thoracic aorta. *Id.* at 54.

The hospital obtained MRI imaging of Petitioner's cervical and thoracic spine. Pet'r Ex. 11 at 85-86. Petitioner was admitted and the next day she was transferred to another hospital, Fort Walton Beach Medical Center. *Id.* at 36-37, 57; Pet'r Ex. 12 at 8-9. The attending physician at that hospital, Dr. Gustavo Ros, noted that the patient's cervical spine MRI was "essentially within normal limits." Pet'r Ex. 12 at 8. He also noted that her thoracic spine MRI "showed a small focal disk protrusion, central, lateralizing slightly to the right at T7 and T8, which w[as] causing effacement of the ventral thecal sac and minimal ventral impression upon the thoracic spinal cord." *Id.* Because no remarkable findings were observed on the thoracic and cervical spine MRIs, Dr.

Ros ordered an MRI of the lumbar spine. The MRI of her lumbar spine reflected a central disc protrusion or possible disc herniation at the L1-L2 level, but no additional significant findings. *Id.* at 105-06.

A consulting doctor, Dr. Roman Kutsy, stated in his report that "[t]he main diagnosis that would be the most rational with [Petitioner's] clinical presentation is [TM]." Pet'r Ex. 12 at 10. However, he noted that "the thoracic spine MRI obtained the day prior was "normal," and although it was done without contrast, "it is not very likely that even [a] non[-]contrast MRI of the thoracic spine would overlook[] [a] lesion of the spinal cord." *Id.* Thus, he opined that there was "no clear neurologic explanation" for Petitioner's symptoms based on his review. Pet'r Ex. 12 at 10. Dr. Kutsy documented that the patient's symptoms occurred acutely the day prior, beginning with an "intense numbing and tingling sensation in her right foot," and progressing "so much that she became non[-]ambulatory." *Id.* at 10-11. He also noted the following:

> [Petitioner] had some vague symptoms for a few days prior to that. Five days ago, while at work, she developed some numbness in the face, which affected primarily [her] mouth and tongue in [a] bilaterally symmetric manner. She "did not feel well" and called her mother and complained of that. For the next few days, she continued to have intermittent problem[s] with generalized fatigue and numbness in the face and mouth, which was symmetric.

Id. Dr. Kutsy ordered an MRI of Petitioner's brain to "rule out MS," suggested follow-up testing based on the results of the pending MRI scans, recommended physical and occupational therapy, and noted that Petitioner's symptoms presented "a very puzzling case." *Id.* at 10. He also wrote that he could not rule out the possibility that Petitioner's "presentation may be . . . psychogenic in nature." *Id.*

The next day, June 26, 2013, Dr. Ros documented that Petitioner reported "feeling better," and that her "[l]ower ext[remity] symptoms and abd[ominal] symptoms [were] resolving." Pet'r Ex. 12 at 37, 39. Dr. Ros further noted that Petitioner was "adamantly refusing [a] lumbar puncture," and that the risks of so refusing were explained to her. *Id.* at 40. That same day, Dr. Kutsy wrote that there was no evidence of spinal cord or nerve root disease or "peripheral neuropathic process" such as Guillain-Barre Syndrome ("GBS"), myopathy, or Multiple Sclerosis ("MS"). *Id.* at 46. The MRI of Petitioner's brain resulted in no significant findings. *Id.* at 104-05. Dr. Kutsy's assessment concluded that Petitioner's "clinical presentation [was] highly suspicious for psychogenic weakness," and he recommended a psychology consultation. *Id.* at 46. On June 28, 2013, Dr. Kutsy documented a diagnosis of "[p]sychogenic leg weakness," as well as an "L1-2 disc protrusion that can not explain all of [Petitioner's] symptoms." *Id.* at 42.

Between June 27, 2013 and July 2, 2013, Dr. Ros continued to document that the patient reported "feeling better," despite continued lower extremity weakness and numbness. Pet'r Ex. 12 at 12-28, 31-33, 41-42. He also wrote that he "[d]iscussed [the] case at length" with another physician, including the possibility of a lumbar disc herniation. *Id.* at 33, 35-36. Petitioner participated in a physical therapy session on June 27, 2013, which she tolerated "fairly well." *Id.* at 109. She was evaluated by the occupational therapy department on July 1, 2013, but she reported to the evaluator that she would not go to an inpatient rehabilitation center, because "she want[ed] to get home to her daughter." *Id.* at 110. Dr. Ros's notes reflect that he ordered a continuation of the same plan of physical therapy during this time period. *Id.* at 12-28, 31-32, 41-42. Petitioner

was discharged from Fort Walton Beach Medical Center on July 3, 2013 with instructions to follow up with a primary care physician and physical therapy. Pet'r Ex. 12 at 48, 95, 221, 226-27.

One day after her discharge from Fort Walton Beach Medical Center, Petitioner reported to the North Okaloosa Medical Center with a urinary tract infection, where a nurse noted her continuing neurological symptoms. Petitioner followed up with a physician, Dr. Kapil Puri, on July 8 and 9, 2013, with continued complaints of urinary retention. Pet'r Ex. 47 at 2-4.

On July 10, 2013, Petitioner again reported to the North Okaloosa Medical Center emergency room with complaints of abdominal pain and inability to urinate or void. Pet'r Ex. 7 at 101. Upon examination, Dr. Martin Mondry noted that Petitioner had been recently hospitalized and diagnosed with a herniated disc, although he documented that she "ha[d] symptoms out of proportion to injury, was 'paralyzed' and continue[d] to have progressive loss of sensation and function." *Id.* at 102. Dr. Mondry and another treating physician at North Okaloosa Medical Center, Dr. Christopher Singley, consulted with other doctors and determined that the patient should be transferred for neurosurgery evaluation at Sacred Heart Hospital. *Id.* at 105-06. Petitioner was transferred to Sacred Heart the same day. *Id.* at 111.

At Sacred Heart, Petitioner was evaluated by Dr. George Dmytrenko. Pet'r Ex. 10 at 8-9. Dr. Dmytrenko wrote that Petitioner's symptoms began approximately June 25, and that she was admitted to Fort Walton Beach Hospital where MRI scans of the brain and lumbosacral spines were performed. *Id.* Dr. Dmytrenko stated that "[s]he was allegedly seen by a neurologist who could not make a diagnosis," and that Petitioner's mother relayed that Petitioner was sent home after being told "this is all in your head." *Id.* Dr. Dmytrenko observed that Petitioner had "improved slightly," but that her strength in her legs was "not nearly what it [wa]s in her arms." *Id.* He also noted that the sensory level remained "at a vague area between the breast and the navel." *Id.* Dr. Dmytrenko reviewed the MRI scans of the brain and lumbar spine from Fort Walton Beach Medical Center, although he wrote that "[t]here was no attempt to obtain an MRI scan of the cervical or thoracic spine."[4] *Id.* at 9. In summary, he stated that Petitioner had a "[TM] type picture, predominantly involving sensory and less so motor components. She has had mild improvement but still has sensory level at about T6 and paraparesis." *Id.* Dr. Dmytrenko ordered MRIs of the cervical and thoracic spine. *Id.* at 23.

The next morning, July 11, 2013, Dr. Dmytrenko wrote in the chart that the MRI scan of Petitioner's cervical spine was normal, but that the MRI scan of her thoracic spine "demonstrate[d] a spindle-shaped area of demyelination and inflammation with a fusiform enlargement of the cord at about T6 through T8." Pet'r Ex. 10 at 7; *see also id.* at 75-76. He outlined a plan to treat the patient with steroids. Pet'r Ex. 10 at 6-7. Dr. Dmytrenko noted that "[t]he major issue at the present time is rehabilitation." *Id.* at 6. On July 13, 2013, Petitioner was discharged to an inpatient rehabilitation center at West Florida Hospital for "intense physical therapy." *Id.* at 6. Her diagnoses at time of discharge were subacute TM, paraparesis, and bowel and bladder dysfunction. *Id.* at 6, 95.

[4] *But see* Pet'r Ex. 11 at 85-86.

Upon admission at West Florida Hospital Rehabilitation Institute, Petitioner reported that she continued to have significant numbness and tingling sensation in both legs that was slowly improving. Pet'r Ex. 19 at 21. She also reported significant bowel symptoms and significant pain, particularly "in the T7-T8 level between the scapula which was intermittent[, but s]he denied any significant weakness of her legs or arms." *Id.* Petitioner received physical and occupational therapy, along with psychological support, while at the facility. *Id.* at 28-82. Petitioner was discharged from West Florida Hospital Rehabilitation Institute on July 30, 2013. *Id.* at 17-20.

Petitioner's medical records reflect that she continued to follow up with various physicians, and continued to have residual symptoms related to her TM, including bowel and bladder problems, pain, and weakness, through at least 2017.[5] *See* Pet'r Ex. 1 at 2-15; Pet'r Ex. 2 at 2-17, 32-45, 77-80; Pet'r Ex. 4 at 2-35; Pet'r Ex. 5 at 3-24; Pet'r Ex. 7 at 2-100; Pet'r Ex. 11 at 1-28; Pet'r Ex. 14 at 2-6; Pet'r Ex. 16; Pet'r Ex. 24; Pet'r Ex. 44; Pet'r Ex. 63.

B. Petitioner's Fact Testimony

Petitioner testified by video teleconference at the hearing and noted that she reviewed her medical records in preparation. Tr. 10. Petitioner testified that in 2013, she "was a healthy 23 year old mom."[6] *Id.* at 11. She described herself as "[f]ully healthy," and testified that she did Zumba three times per week and walked in the morning. *Id.* Petitioner testified that she worked full-time and went to school full-time at night. *Id.* She was training to be a medical assistant. *Id.* As part of that training, she was required to complete an externship. *Id.* In preparation for the externship, she was required to receive the series of Hep B vaccinations. *Id.* at 11-12. Petitioner recalled receiving Hep B vaccines in October 2012, November 2012, and April 2013. *Id.* at 12.

Petitioner testified that "about five days or more, give or take," before June 24, 2013, she "wasn't feeling good that whole entire weekend." Tr. 15. Petitioner stated that she "was sleeping all weekend, which is nothing like [her]." *Id.* She explained that she is usually "out doing something with [her] daughter or something with friends," but "[a]ll [she] wanted to do was sleep." *Id.* at 15-16. At that time, she was working at Dunkin' Donuts. *Id.* at 15. Petitioner stated that she was sent home early from a shift at Dunkin' Donuts "because [she] was having facial numbness, blurriness, [and] headaches[; she] just wasn't feeling good at all that weekend." *Id.* The timeline of these symptoms is somewhat uncertain, as Petitioner also agreed with her counsel that these symptoms occurred "a few days before" and "in the middle of the week" before her admission to Twin Cities Hospital on Monday, June 24, 2013. *Id.* at 16.

Petitioner stated that she began working as a urology medical assistant only days before she became ill. Tr. 12. She explained that she completed training at a doctor's office on a Friday, June 21, 2013, and returned the following Monday to begin working. *Id.* at 13. Petitioner described the initial onset of her symptoms June 24, 2014 as follows:

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[5] Respondent "agrees that [P]etitioner had more than six months of residual effects or complications of her injury after vaccination." Resp't's Rept. at 8, ECF No. 44.

[6] Petitioner testified that she now has two children, ages one and seven. Tr. 10-11.

> [T]hat morning, I started getting dizzy [and] I had a headache. So I kept going to the bathroom, splashing water on my face, trying to see if it was just anxiety or nerves from the first day of the actual job.

Id. Petitioner explained that the medical office was transitioning from paper charts to electronic charts, so she was on a stepladder that morning moving boxes. *Id.* She described the progression of her symptoms over that morning as follows:

> [W]hen I was up on the stepladder, my right foot started going numb, like it was going to sleep[,] and I kept trying to shake it off and just keep going. And then they bought us lunch because we were preparing for the new system. And when I sat down for lunch, my leg was still numb, but then my waist and abdomen started going numb, and I couldn't see. I had blurry vision [and] a headache. And I was texting my mom and asking if this is normal or if it was anxiety.

Id. After being unable to eat anything at lunch, Petitioner testified that she "started walking back towards [her] office and [she] had [her] hand on the wall because [her] legs were going numb and [she] couldn't walk properly." *Id.* at 13-14. Petitioner recalled that a coworker told her that she did not look well. *Id.* at 14. That coworker ultimately brought Petitioner to the hospital nearest the office, Twin Cities Hospital. *Id.*

Petitioner estimated that "the incident started" around 10:30 a.m. that morning, and that she arrived at Twin Cities Hospital at "about 11:00" a.m. Tr. 14. Petitioner testified that "by the time [she] got [to the hospital], [she] was completely paralyzed [and] couldn't move." *Id.* She testified that she was admitted to the hospital and tests were completed. *Id.* Petitioner testified that she was at Twin Cities Hospital until approximately midnight that night, when she was transferred to Fort Walton Hospital. *Id.* at 14-15.

At Fort Walton Hospital, Petitioner recalled being treated by Dr. Roman Kutsy and describing her symptoms from the previous week to him. Tr. 15. Petitioner testified that providers at Fort Walton Hospital "gave [her] an incorrect diagnosis," and she was discharged on July 3, 2013. *Id.* at 15-16.

Petitioner testified that about twelve hours after she was discharged from Fort Walton Hospital, she went to Crestview Hospital because she was unable to urinate. Tr. 16. She testified that she was catheterized at that hospital and diagnosed with a severe urinary tract infection. *Id.* Petitioner stated that she was discharged with a catheter in place and was told to follow up with a doctor for the urinary symptoms. *Id.*

Petitioner testified that she "ended up back in the hospital by ambulance on July 10th," 2013. Tr. 17. She explained that she "started out at Crestview Hospital," where providers ran numerous tests. *Id.* Petitioner testified that, based on "a blood test that c[a]me back . . . show[ing] markers of something wrong," she was transferred to Sacred Heart Hospital. *Id.* Petitioner described that, by that time, her symptoms included "paralyzation[;] neurogenic bladder[;] neurogenic bowels[;] pain in [her] back[;] numbness[;] tingling[;] fatigue[;] and all of that." *Id.* She recalled that Dr. George Dmytrenko, a neurologist at Sacred Heart Hospital, "did the MRI with the contrast and found the lesion from T6 to T8 in [her] spine." *Id.* at 17-18. She testified that Dr. Dmytrenko diagnosed her with TM. *Id.*

Petitioner explained that, "shortly after that," she was released to the West Florida Rehabilitation Center. Tr. 18. At the Rehabilitation Center, she was taught "how to live with the transverse" myelitis. *Id.* This included training her how to self-catheterize, how to use a wheelchair, how to walk with aids, and how to do exercises and therapy to gain muscle control. *Id.* Petitioner testified that when she was released from the Rehabilitation Center, she "was still in the wheelchair." *Id.* at 18-19. She explained that she "could only probably walk about 200 feet without falling or having an accident" at that time. *Id.* at 19. She estimated that it took "about a year" to become fully independent of walking aids. *Id.* at 18-19.

Petitioner testified that she still has neurogenic bladder and bowels, and still needs to self-catheterize. Tr. 19. She stated that she has chronic fatigue, chronic migraines, "dizziness every now and then, [and] neuropathy from the breast line down." *Id.* She also testified that she does not have sensitivity to hot or cold. *Id.* Additionally, Petitioner testified that she "still ha[s] muscle spasms, which cause [her] to fall very frequently." *Id.* Petitioner testified that she has also developed hypothyroidism and a cyst on her brain. *Id.* at 20. She treats regularly with several different doctors, including Dr. Nagrani for her hypothyroidism and frequent kidney infections; Dr. Coates for obstetrics and gynecology; Dr. Mendez for primary care; and neurologist Dr. Aubert, who monitors the cyst on her brain and treats the TM. *Id.*

Petitioner testified that she will not be able to work in the future as a medical assistant "because of [her] immune[e] system being compromised." Tr. 19. Additionally, she is "a fall risk" with chronic back pain. *Id.* Consequently, she cannot spend long hours on her feet or lift patients. *Id.* She testified that she is not currently working. *Id.* at 10.

III. Expert Review

A. Petitioner's Expert, Ahmet Höke, M.D., Ph.D, FRCPC

Dr. Ahmet Höke ("Dr. Höke") authored two expert reports in this case and testified at the hearing. Pet'r Exs. 28, 50; Tr. 22-69, 153-57. Dr. Höke is currently a professor of neurology and neuroscience at Johns Hopkins University School of Medicine. Pet'r Ex. 28 at 2; Pet'r Ex. 29 at 1. He testified that he is board-certified in neurology. Tr. 22. Dr. Höke testified that approximately seventy percent of his time is spent on research, and the other twenty-five to thirty percent is spent on clinical and administrative duties. *Id.* at 24-25.

Dr. Höke testified that his research focuses on "peripheral nerve regeneration and understanding mechanisms of peripheral neuropathies." Tr. 23. Dr. Höke estimated that he has published more than 140 papers. *Id.*; *see* Pet'r Ex. 29 at 2-11. Although he has "not specifically published research articles on transverse myelitis," he has written book chapters on related autoimmune peripheral neuropathies, specifically GBS and Chronic Inflammatory demyelinating Polyneuropathy ("CIDP"). Pet'r Ex. 28 at 2.

Dr. Höke's clinical practice is limited to patients with peripheral neuropathies. Pet'r Ex. 28 at 2. Dr. Höke testified that he sees "probably a couple hundred patients a year" in clinic at Johns Hopkins, most of whom are peripheral neuropathy patients. Tr. 23-24. He explained that

he "see[s] a fair amount of patients with either acute GBS or GBS patients who are not recovering from their GBS[, as well as] many patients with CIDP." Pet'r Ex. 28 at 2. He also "attend[s] on the inpatient general neurology ward service one month [per] year where [he] see[s] and manage[s] patients with [TM]." *Id.* Dr. Höke explained that Johns Hopkins has "a specialized center for [TM]," so there are "quite a few inpatients." Tr. 24. He estimated that he has "managed more than 40 patients with [TM]." Pet'r Ex. 28 at 3.

Dr. Höke testified that he "[r]arely" participates in legal medical cases. Tr. 25. He stated that he has participated in twenty-two cases in the vaccine program in the last twelve or thirteen years, with his participation in nineteen of those cases being for a petitioner. *Id.* Dr. Höke also stated that he has testified in Vaccine Program cases on two occasions; once for a petitioner and once for Respondent. *Id.*; Pet'r Ex. 28 at 3. Dr. Höke was admitted to offer expert testimony at the hearing in the area of neuromuscular neuroscience. Tr. 26.

i. Dr. Höke's First Report

Dr. Höke's first expert report was authored on August 2, 2015. Pet'r Ex. 28. In preparation for the report, Dr. Höke reviewed Petitioner Exhibits 1-27. *Id.* at 1-2. He began his report with a brief review of Petitioner's medical records. *Id.* at 3-4. His review is generally consistent with the exhibits in the record beginning June 24, 2013. *Id.* Notably, Dr. Höke did not reference any symptoms occurring prior to June 24, 2013 that he associated with Petitioner's TM. *See id.* Additionally, Dr. Höke wrote that he would discuss Petitioner's diagnoses and "possible relationship to the hepatitis B vaccinations she had on 10/15/2012 and 04/18/2013," so it is unclear whether Dr. Höke was aware of the additional Hep B vaccination in November 2012. *Id.* at 3.

After summarizing Petitioner's medical records, Dr. Höke opined that the records "clearly indicate[] that [Petitioner] had an acute episode of myelitis." Pet'r Ex. 28 at 4. He notes that her presentation of "upper abdominal pain associated with rapidly evolving weakness in the lower extremities, a thoracic sensory level[,] and bowel and bladder dysfunction are almost textbook classic for [TM]." *Id.* He acknowledges that the diagnosis was initially unclear, but that it was confirmed with MRI imaging, which showed a lesion "at the appropriate level (T6-T8)." *Id.*

Dr. Höke described idiopathic TM as "an inflammatory disease affecting the spinal cord." Pet'r Ex. 28 at 4 (citing Pet'r Ex. 34[7]). He explained that "[s]ymptoms and examination findings vary depending on the level and the extent of inflammation," but they generally involve a combination of motor pathways, sensory fibers, and autonomic dysfunction. *Id.* at 4-5. He wrote that "case series [have] show[n] close association between infections and/or vaccinations and [TM]." *Id.* at 5. Dr. Höke noted that "[d]ifferential diagnoses include[:] demyelinating diseases of the central nervous system, such as multiple sclerosis [ ], neuromyelitis optica[,] and idiopathic

[7] Bruce A. C. Cree, *Acute Inflammatory Myelopathies*, Multiple Sclerosis and Related Disorders 613 (Douglas S. Goodin, ed., 3d Series, 2014).

[TM;] infections[,] such as herpes viruses or tuberculosis[;] and other inflammatory diseases[,] such as neurosarcoidosis or systemic lupus erythematosus." *Id.* at 4 (citing Pet'r Ex. 35[8]).

Dr. Höke summarized two papers where different authors studied a potential relationship between vaccines and TM. Pet'r Ex. 28 at 5. He first discussed one paper from 2009, wherein the authors, Agmon-Levin, et al., conducted a "large multi-analysis review of the literature" to identify "reported cases of [TM] which were temporally associated with various vaccines." *Id.* (citing Pet'r Ex. 30[9]). Dr. Höke wrote that, in that study, the authors identified thirty-seven reported cases of TM which were temporally associated with several vaccines, including vaccines for Hep B. *Id.* Dr. Höke noted that "[i]n most cases[,] the onset was from a few days to 3 months." *Id.* Dr. Höke then referenced another paper, from 2001, which he called "one of the strongest case series that showed a close temporal relationship between [the] Hep[] B vaccine and acute [TM]." *Id.* (citing Pet'r Ex. 36[10]). Dr. Höke summarized that the authors of that paper, Karaali-Savrun, et al., identified four cases of acute TM which developed after the patients received a Hep B vaccination. *Id.* He noted that three of the patients developed symptoms within three to four weeks of vaccination, but the fourth patient "developed neurological symptoms about 3 months after the third dose" of the vaccine. *Id.*

Dr. Höke wrote that "[t]he pathogenic mechanism of acute [TM] is not exactly known[,] but it is thought to be an autoimmune phenomenon related to [a] molecular mimicry hypothesis." Pet'r Ex. 28 at 5 (citing Pet'r Ex. 33[11]). Dr. Höke cited to a 2004 paper where the authors, Krishnan, et al., discussed the "more established link between molecular mimicry and another monophasic autoimmune neurological disorder, Guillain-Barre syndrome, a demyelinating disease affecting the peripheral nerves." *Id.* (citing Pet'r Ex. 37[12]). He explained that the authors of that paper pointed to other research which showed "that in [TM,] molecular mimicry may activate T-cell based autoimmunity [ ] or stimulate generation of auto-antigens [ ] that result in immune

[8] Anu Jacob & Brian G. Weinshenker, *An Approach to the Diagnosis of Acute Transverse Myelitis*, 28 SEMINARS IN NEUROLOGY 105 (2008).

[9] N. Agmon-Levin, S. Kivity, M. Szyper-Kravitz & Y. Shoenfeld, *Transverse Myelitis and Vaccines: A Multi-Analysis*, 18 LUPUS 1198 (2009).

[10] F. Karaali-Savrun, A. Altintas, S. Saip & A. Siva, *Hepatitis B Vaccine Related-Myelitis?*, EUR. J. OF NEUROLOGY 711 (2001).

[11] Amer Awad & Olaf Stüve, *Idiopathic Transverse Myelitis and Neuromyelitis Optica: Clinical Profiles, Pathophysiology and Therapeutic Choices*, 9 CURRENT NEUROPHARMACOLOGY 417 (2011).

[12] Chitra Krishnan, Adam I. Kaplin, Deepa M. Deshpande, Carlos A. Pardo & Douglas A. Kerr, *Transverse Myelitis: Pathogenesis, Diagnosis and Treatment*, 9 FRONTIERS IN BIOSCIENCE 1483 (2004).

complex formation and activation of cell- or complement[-] mediated self[-]injury to neural tissues." *Id.* (citing Pet'r Exs. 38,[13] 39,[14] 42[15]).

Dr. Höke then explained that "[t]he issue of molecular mimicry is amplified when both B-cells (via the antibodies they produce) and auto-reactive T cells act in concert." Pet'r Ex. 28 at 5. He wrote that "T-cell receptors can recognize a broad range of epitopes." *Id.* Therefore, Dr. Höke explained that it is "even easier for T-cell receptors to be activated by cross-reactivity with epitopes found on infectious agents or vaccine components derived from the infectious agents" when major histocompatibility complex binding motifs are degenerated. *Id.* Dr. Höke wrote that "[e]xamples of molecular mimicry in neurological disease with auto-reactive T-cells include establishment of a rabbit model of multiple sclerosis using hepatitis B virus polymerase peptide." *Id.* He also noted that "[s]imilar examples for other autoimmune disorders also exist (e.g. experimental anti-phospholipid syndrome)." *Id.*

Dr. Höke wrote that "[i]t is generally accepted that in order to elicit an autoimmune response, the infection or vaccine has to be closely temporally associated and precede the neurological event by a few days to 6-8 weeks." Pet'r Ex. 28 at 5. That timeline is "based on the observation that it takes [a] few days to generate antibodies against components of an infectious agent (in B-cell mediated autoimmunity) or create autoreactive T-cells (in T-cell based autoimmunity)." *Id.* Citing a book chapter available on the World Health Organization's website, Dr. Höke wrote that "the initial response to vaccine starts within days and peaks around four weeks." *Id.* at 6 (citing Resp't Ex. I[16] at 9, Figure 2.3). Therefore, Dr. Höke concludes that "the onset of [Petitioner's] neurological symptoms about 2 months after her second [sic] hepatitis B vaccine would fit into a proper immune response timeframe." Pet'r Ex. 28 at 6.

Dr. Höke concluded that be "believe[s] [Petitioner] developed acute [TM] most likely as a consequence of her Hep[] B vaccination." Pet'r Ex. 28 at 6. He emphasized that Petitioner's clinical presentation, MRI results, and clinical course upon discharge support the diagnosis of TM. *Id.* He wrote that the "[c]lose temporal relationship between her vaccination and development of

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[13] Michael C. Levin, Sang Min Lee, Franck Kalume, Yvette Morcos, F. Curtis Donhan Jr, Karen A. Hasty, Joseph C. Callaway, Joseph Zunt, Dominic M. Desiderio & John M. Stuart, *Autoimmunity Due to Molecular Mimicry as a Cause of Neurological Disease*, 8 NATURE MED. 509 (2002).

[14] Julie K. Olson, Todd N. Eagar & Stephen D. Miller, *Functional Activation of Myelin-Specific T Cells by Virus-Induced Molecular Mimicry*, 169 J. OF IMMUNOLOGY 2719 (2002).

[15] R. Anthony Williamson, Mark P. Burgoon, Gregory P. Owens, Omar Ghausi, Estelle Leclerc, Louise Firme, Sharon Carlson, John Corboy, Paul W. H. I. Parren, Pietro P. Sanna, Donald H. Gilden & Dennis R. Burton, *Anti-DNA Antibodies are a Major Component of the Intrathecal B Cell Response in Multiple Sclerosis*, 98 PNAS 1793 (2001).

[16] Claire-Anne Siegrist, *Vaccine Immunology*, *in* PLOTKIN'S VACCINES 16 (7th ed. 2018). Although Dr. Höke only provided a link to this chapter in his expert report, Respondent filed the document after the hearing.

[TM], previous case reports, and the 'molecular mimicry' hypothesis make it very likely that her [TM] is due to the Hep[] B vaccination." *Id.*

ii. Dr. Höke's Second Report

Dr. Höke's second expert report was authored on July 4, 2016. Pet'r Ex. 50. In preparation of his second report, Dr. Höke reviewed Respondent's expert's report, Respondent's expert's CV, and the medical literature filed by Respondent. *Id.* at 1. Dr. Höke opined in his second report that he and Respondent's expert agree on the diagnosis of TM. *Id.* He concluded that the "disagreement seems to center around the issue of causality with relation to [Petitioner's] vaccination with [the] Hep[] B vaccine." *Id.*

Dr. Höke acknowledged that case reports and aggregate reports "do not establish a direct causality." Pet'r Ex. 50 at 1. However, Dr. Höke wrote that for "rare diseases such as [TM], establishment of a direct link with a risk factor is not straightforward." *Id.* Additionally, "in many instances[,] [direct causality] has not been studied in detail." *Id.* Dr. Höke wrote that "[d]espite their many faults, case reports do teach us about a potential association between a risk factor and a disease." *Id.* Dr. Höke noted that "in a given patient[,] it would be difficult to ascertain with 100% certainty that a given risk factor is not causally linked to the disease phenotype." *Id.*

Dr. Höke wrote that, after he authored his first report, a new case report was published which "potentially link[s]" the Hep B vaccine and neuromyelitis optica ("NMO"). Pet'r Ex. 50 at 1 (citing Pet'r Ex. 52[17]). He describes NMO as "a disease that is a combination of [TM] and optic neuritis." *Id.* He also referenced four additional case reports, not cited in his first report, which "show a potential association between [the Hep B vaccine] and demyelinating diseases of the central nervous system." *Id.* at 2 (citing Pet'r Exs. 54,[18] 55,[19] 57,[20] 60[21]).

[17] Richard Heekin, Chetan Gandhy & Derrick Robertson, *Seronegative Neuromyelitis Optica Spectrum Disorder Following Exposure to Hepatitis B Vaccination*, 7 CASE REP. NEUROLOGY 78 (2015).

[18] Owen Stewart, Bernard Chang & John Bradbury, *Simultaneous Administration of Hepatitis B and Polio Vaccines Associated with Bilateral Optic Neuritis*, 83 BRIT. J. OPHTHALMOLOGY 1200 (1999).

[19] Lisa M. Tartaglino, Terry Heiman-Patterson, David P. Friedman & Adam E. Flanders, *MR Imaging in a Case of Postvaccination Myelitis*, 16 AM. J. NEURORADIOLOGY 581 (1995).

[20] Vesna V. Brinar & Charles M. Poser, *Disseminated Encephalomyelitis in Adults*, 110 CLINICAL NEUROLOGY & NEUROSURGERY 913 (2008).

[21] Franco Trevisani, Guido Castelli Gattinara, Paolo Caraceni, Mauro Bernardi, Francesco Albertoni, Roberto D'Alessandro, Luigi Elia & Giovanni Gasbarrini, *Transverse Myelitis Following Hepatitis B Vaccination*, 19 J. HEPATOLOGY 317 (1993).

Dr. Höke also disagreed with several "summary statements" referenced in Respondent's expert's report which are quotes from the National Multiple Sclerosis ("MS") Society and the Institute of Medicine related to the risk of MS after the Hep B vaccine. Pet'r Ex. 50 at 2 (referring to Resp't Ex. A at 4-5). Dr. Höke explained that MS is "a more common demyelinating disease of the central nervous system." *Id.* Dr. Höke wrote that a systematic review of the literature, which was completed more recently than when the quoted statements were made by the National MS Society and the Institute of Medicine, reveals a connection between the Hep B vaccine and MS. *Id.* (citing Pet'r Ex. 59[22]). He explained that "although several studies did not show an increased risk for development of demyelinating disease with [the Hep B vaccine], one prospective study clearly showed a 3.1 fold increase in development of MS in patients who received" the Hep B vaccine. *Id.* (citing Pet'r Ex. 58[23]). Dr. Höke wrote that the study "was based on looking at the incidence of MS in the General Practice Research Database (GPRD) in Britain," which consists of "over 3 million patients." *Id.* The study then "compar[ed] the characteristics of patients diagnosed with MS and controls," and Dr. Höke noted that "10 control cases were reviewed for each MS diagnosis." *Id.* Dr. Höke wrote that "[t]he analysis showed that patients in the general population were 3.1 times more likely to have developed MS if they received [the Hep B vaccine] within 3 years of the onset of their MS." *Id.* Thus, Dr. Höke explained that "the link between [the Hep B vaccine] and demyelinating diseases of the central nervous system is not straightforward and the potential link has not been conclusively demonstrated not to exist." *Id.*

In conclusion, Dr. Höke wrote that "although there may not be [ ] direct conclusive epidemiological data to link [the] [H]ep[] B vaccine to [TM], several studies do show a link between [the] [H]ep[] B vaccine and other demyelinating diseases of the central nervous system." Pet'r Ex. 50 at 2. Therefore, he concluded that, "given a theoretical framework for molecular mimicry and autoimmunity, one cannot be sure if there is no causative link between the two." *Id.*

iii. Dr. Höke's Testimony

Dr. Höke stated that TM is a "relatively rare disorder," and explained that patients with TM "may experience a variety of symptoms depending on whether the motor or sensory pathways are affected, as well as bowel and bladder dysfunction." Tr. 27-28. He testified that although the medical community does not know exactly why TM occurs in some patients, the "underlying process is thought to be an autoimmune attack on the myelin component of the central nervous system with an inflammation that results in neurological dysfunction." *Id.* at 28. Dr. Höke explained that diagnosis of TM is made through clinical presentation, neurological examination, imaging studies, and sometimes spinal fluid analysis. *Id.* at 30. Dr. Höke explained that TM "is considered to be a monophasic illness," where the patient suffers "only one attack." *Id.* at 28-29. In contrast, related diseases like MS are thought to be relapsing and remitting, with multiple lesions separated by space and time. *Id.* at 29.

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[22] V. Martínez-Sernández & A. Figueiras, *Central Nervous System Demyelinating Diseases and Recombinant Hepatitis B Vaccination: A Critical Systemic Review of Scientific Production*, 260 J. NEUROLOGY 1951 (2013).

[23] Miguel A. Hernán, Susan S. Jick, Michael J. Olek & Hershel Jick, *Recombinant Hepatitis B Vaccine and the Risk of Multiple Sclerosis: A Prospective Study*, 63 NEUROLOGY 838 (2004).

Dr. Höke testified that "autoimmune diseases, especially the demyelinating autoimmune diseases of the central nervous system[,] are more common among women." Tr. 29. Additionally, he testified that demyelinating disorders are most common in women in their twenties and thirties. *Id.* at 30. He testified that certain infections can also cause TM. *Id.* at 29. In fact, Dr. Höke testified that "the risk of developing [TM] is probably higher with the actual infection [of Hep B] than with the vaccination." *Id.* at 49.

Dr. Höke testified that in the "literature on many autoimmune diseases[,] the primary hypothesis is that there is a molecular mimicry between the antigen that incites the initial antibody response, as well as another component within the person's body." Tr. 32. He noted that this could happen "in the nervous system or any other tissue," where "there is a homology that creates an opportunity for the antibody to go and attack [a person's] own proteins or lipids or sugar moiety and their tissues." *Id.* Dr. Höke testified that for molecular mimicry to occur, there must be an "antibody presence or active T cells." *Id.* at 36.

Dr. Höke testified that, in the medical community in general, molecular mimicry is considered to be a biologically plausible mechanism for demyelinating disorders. Tr. 33. He further testified that molecular mimicry is "considered a hypothesis that is well supported by the experimental models, mostly in the peripheral nervous system, but also in the central demyelinating diseases." *Id.* Dr. Höke acknowledged that the literature underlying his molecular mimicry hypothesis primarily involves GBS. *Id.* at 32. Dr. Höke explained that GBS is "a disease of the peripheral nerves," and patients sometimes have "symptoms very similar to [TM]." *Id.* at 64. Dr. Höke explained that GBS is "probably the most well studied experimentally of all autoimmune diseases of the nervous system." *Id.* at 63. He testified that there are "very good animal models" relating to GBS, and "the molecular mimicry hypothesis was really proven within the GBS literature." *Id.* This is because the medical community "know[s] exactly what the inciting factor is and how it corresponds to a similar molecule on the nervous tissue." *Id.* at 32-33; *see also id.* at 63. Therefore, Dr. Höke explained that with GBS, medical experts know how the identified antibody "makes [a] mistake and goes and attacks a corresponding molecule on the nervous tissue." *Id.* at 63. Dr. Höke testified that in MS and TM, the hypothesis is that "there is a similar process," but medical experts "just don't know what that protein is[,] or lipid is[,] or sugar moiety is." *Id.* He testified that although GBS affects the peripheral nervous system and TM affects the central nervous system, an autoimmune reaction resulting from a vaccine would occur in the same way. *Id.* at 64.

Dr. Höke explained that when a vaccine is administered, it causes an antibody response against the antigen that is present in the vaccine, which helps prevent future infections. Tr. 27. The Hep B vaccine, therefore, is designed to prevent development of a hepatitis B infection by causing an antibody response similar to that which would occur with such an infection. *Id.* Dr. Höke explained that in some patients, "in the appropriate environment with the antibody response, those antibodies can get access to the spinal cord and cause [TM]." *Id.* at 32.

Dr. Höke noted that the development of TM is "obviously not just due to the vaccine[,] [because] [o]therwise, we would be seeing [TM] in every patient." Tr. 32. Dr. Höke opined that, "especially for [central nervous system] demyelinating diseases, there is probably a secondary

event that triggers the access of those antibodies to the central nervous system to induce the neurological damage." *Id.* at 36. Although he noted that "often, especially for [central nervous system] diseases, there [has] to be a secondary insult," he conceded that the medical community has not pinpointed that secondary insult. *Id.* at 46. Dr. Höke explained that "[t]here has to be [an] opening of the blood-brain barrier to allow access of the antibodies to -- or the cells -- inflammatory cells to access the central nervous system to induce the demyelination." *Id.* He testified that the secondary insult could be "a trauma," or it could be that "some people's genetic makeup makes their blood-brain barrier more leaky." *Id.* at 46-47.

Dr. Höke specifically discussed several published papers cited by himself and Respondent's expert which address a potential connection between Hep B and TM. Dr. Höke acknowledged that some of the studies he referenced looked at patients who received the Hep B vaccine in combination with other vaccines. Tr. 53. He conceded that the presence of another vaccine in a studied patient could mean that the Hep B vaccine did not cause the reaction which was studied. *Id.* at 51-52.

He explained that the Karaali-Savrun paper is a case report reflecting "four cases of [TM] after [H]ep[] B vaccination," where patients with "no other risk factors . . . developed [TM] soon after receiving the [H]ep[] B vaccine." Tr. 34; Pet'r Ex. 36. He noted that the authors of that paper "put forth the hypothesis that [the findings] could be due to the molecular mimicry mechanism." Tr. 34.

Dr. Höke also described the Agmon-Levin paper. Pet'r Ex. 30. He testified that it represents "a broader summary of reviewing the literature and putting together all the case reports," where thirty-nine cases of TM occurring after a hepatitis B infection were reviewed. Tr. 34.

Dr. Höke opined that the 2004 Hernán paper "was really well done." Tr. 34; Pet'r Ex. 58. He testified that the paper looked at the incidence of MS after Hep B vaccine in the general population, using data from general practice. Tr. 34. Dr. Höke described the process of the "prospective nested case control study," which "looked at over 3,000 patients and identified several hundred MS patients [and then] compared them to controls." *Id.* at 34-35. Dr. Höke testified that "[f]or each indexed patient with [MS], [the researchers] identified at least ten cases without MS, and then looked at their risk factors." *Id.* at 35. Dr. Höke explained that the researchers initially hypothesized "that if [a patient] had vaccinated with hepatitis B in the previous three years, their incidence of MS [would be] higher." *Id.* He testified that the research showed "a threefold increase in incidence." *Id.*

Dr. Höke also discussed the Shaw paper, which was cited by Respondent's expert. Tr. 39; Resp't Ex. C.[24] Although the paper, which was based on a study of VAERS data, did not find an increased risk for MS after Hep B vaccination, Dr. Höke testified that "VAERS is notorious for

[24] Frederic E. Shaw, Jr., David J. Graham, Harry A. Guess, Julie B. Milstein, Joyce M. Johnson, Gary c. Schatz, Stephen C. Hadler, Joel N. Kuritsky, Elizabeth E. Hiner, Dennis J. Bregman & James E. Maynard, *Postmarketing Surveillance for Neurologic Adverse Events Reported After Hepatitis B Vaccination*, 127 AM. J. EPIDEMIOLOGY 337 (1988).

underreporting." Tr. 39. Therefore, he testified, finding an epidemiological association based on VAERS reports "is going to be difficult." *Id.* Dr. Höke's believes that the 2004 Hernán paper, cited by him, is "a much stronger paper." *Id.* at 40. Dr. Höke testified that he was unaware that Hernán authored a second paper in 2006. *Id.* at 55-56; *see* Resp't Ex. J.[25]

Dr. Höke testified that he does not believe that Respondent's expert disagrees "about whether molecular mimicry can be a mechanism for autoimmunity." Tr. 38. Instead, Dr. Höke opined that "the disagreement stems from the timing of the process." *Id.* Dr. Höke initially testified that "usually[,] the antibody production peaks around two to four weeks." *Id.* at 35. Referring to the period of time where a patient is at risk of developing an autoimmune response, Dr. Höke also testified that "we generally consider [a period of] four weeks or eight weeks." *Id.* at 62. He also testified that experts "generally accept 8 weeks -- 8 to 12 weeks as a standard period where you can see autoimmunity because that's the peak of the autoimmune response." *Id.* at 37. Dr. Höke acknowledged that some of the studies that he referenced in support of his theory discussed symptoms that started within a month of vaccination. *Id.* at 49-50.

Dr. Höke agreed that "for policy purposes, we may need to create some sort of a cutoff," but he opined that "eight weeks is too stringent." Tr. 65. Dr. Höke testified that in "broad population-based studies, [researchers are] always looking at the majority of the patients." *Id.* at 38. He explained that "the peak is when the majority of patients are going to present[,] [b]ut there are always individual patients who will probably fall outside that range." *Id.* at 65. He explained that there is often "going to be a two standard deviation [range] that [is] the statistically accepted norm," but "there [are] going to be patients who are beyond that." *Id.* at 51; *see also id.* at 38-39. In other words, although the studies must create a cutoff date between "when the risk is high and when the risk is low," it is "an artificial cutoff." *Id.* at 39, 61-62. He explained that, for any given individual patient, it is difficult to apply such a stark cutoff, "especially when the dates are so close to each other." *Id.* at 39. For example, "if the cutoff is 60 days . . . and you have somebody who probably had similar levels of antibodies on Day 62[,] [that person] could easily have developed [TM] within that time frame." *Id.* at 42. Dr. Höke opined that "when you're taking care of [any individual patient,] there are so many other variables that may not be obvious in an epidemiological study." *Id.* at 40. He explained that, "in some people, the immune response is really hyperactive and it can present very, very rapidly." *Id.* at 65. However, in other people, "it may take a lot longer," he explained. *Id.* He testified that he believes "it's luck" that determines when a patient has a reaction. *Id.* at 65-66. Dr. Höke emphasized that "human biology is not like a mechanical event where you have a clear cutoff between one event and another. Some people's bodies just react differently." *Id.* at 68. He explained that "we just don't know" why the antibody response happens when it does in any specific patient. *Id.* at 66.

Additionally, Dr. Höke emphasized that even after the antibody response peaks, "it will taper down[,] [b]ut it doesn't go away." *Id.* at 35. He stated that "as long as you have high levels of circulating antibodies, that process [of molecular mimicry] can happen [at] any time." *Id.* at 36. Dr. Höke opined that it is "naïve to think that you could have autoimmunity up to week 8, but then one day later, you can't have autoimmunity," even though "your antibody titers are probably the

[25] Miguel A. Hernán & Susan S. Jick, *Hepatitis B Vaccination and Multiple Sclerosis: The Jury is Still Out*, 15 PHARMACOEPIDEMIOLOGY & DRUG SAFETY 653 (2006).

same." *Id.* at 37. He testified that there is an "elevated risk for a much longer period of time," and that "antibody levels don't trail off or fall off the cliff" on a particular date. *Id.* at 43-44. Dr. Höke emphasized that "antibodies don't go away on day 61[;] [the antibody level] still remains elevated." *Id.* at 38. Dr. Höke testified that the titer levels are "exponentially higher" than a patient's baseline level, even four months after vaccination. *Id.* at 66. He elaborated that "there's probably not a significant difference between four weeks and 16 weeks." *Id.* at 67.

Dr. Höke testified that in one study, researchers found that "the levels of the antibody response among patients who received [a] [H]ep B vaccine" were not statistically significantly different between weeks eight and sixteen. Tr. 35-36; Resp't Ex. H at 4.[26] He testified that even at week sixteen, "the antibody levels were profoundly elevated compared to [the level measured] before [the patients] received the [H]ep B vaccine." Tr. 36. He noted that the researchers did not measure the levels after sixteen weeks. *Id.* Additionally, Dr. Höke testified that levels remain elevated for months. *Id.* at 43. Dr. Höke also testified that the World Health Organization "usually cites a period of two to three months for the onset of neurological disease," citing the Karaali-Savrun paper. *Id.*; Pet'r Ex. 36 at 4. He also noted that the Hernán paper discussed studies where MS was not present within one year after vaccination, but within two years it developed at increased ratios when compared with non-vaccinated patients. Tr. 43-44; Pet'r Ex. 58. Referring to Figure 2.3 in the Siegrist article, Dr. Höke testified that, after the first dose of a vaccine, the antibody response rises and then comes back down fairly quickly. Tr. 58; Resp't Ex. I at 9, Figure 2.3. After a booster vaccination, he testified that the antibody response rises "higher than the initial level" and then remains higher than baseline for an extended period of time. Tr. 59. Dr. Höke explained that after the peak immune response after a booster vaccination, the data "clearly shows that [a patient has] very high levels of antibody response six months out and even much longer . . . with certain vaccinations." *Id.* at 54; Resp't Ex. I at 9, Figure 2.3. Dr. Höke testified that "the reason we do it [give booster vaccinations] is [a person] get[s] an antibody response that lasts for years." Tr. 54. He testified that "as long as there [are] elevated antibody levels in the blood, [a patient is] going to be at risk." *Id.* at 46.

Dr. Höke testified that the Baxter paper[27] was "not specifically addressing [H]ep B and TM or [H]ep B and MS." Tr. 153. Instead, he explained that the study involved "a whole compilation of vaccines." *Id.* Although Dr. Höke opined that the study "is a fairly well done study because it looks at a very large patient population," he noted that the validity of the study relies on the codes entered by physicians. *Id.* at 154. Dr. Höke explained that the study only considered diagnostic codes for idiopathic TM and ADEM, which would potentially miss patients who presented with milder symptoms, such as "numbness or maybe paresis and not clear-cut [TM]." *Id.* It would also

[26] Mohammad Reza Sam, Mohammad Ali Shokrgozar & Fazel Shokri, *Longitudinal Determination of Hepatitis B surface Antigen-Specific B Lymphocyte Frequency in Healthy High Responder Adults After Booster Vaccination*, 51 INTERVIROLOGY 87 (2008).

[27] The Baxter paper, Respondent Exhibit L, was introduced during Respondent's expert's testimony, and Dr. Höke addressed it when recalled. Roger Baxter, Edwin Lewis, Kristin Goddard, Bruce Fireman, Nandini Bakshi, Frank DeStefano, Julianne Gee, Hung Fu Tseng, Allison L. Naleway & Nicola P. Klein, *Acute Demyelinating Events Following Vaccines: A Case-Centered Analysis*, 63 CLINICAL INFECTIOUS DISEASES 1456 (2016).

potentially exclude patients such as Petitioner, whose diagnosis "was missed for a long time." *Id.* at 155.

Dr. Höke testified that Petitioner "was a previously healthy person [and] had no other neurological illness." Tr. 37-38. He also noted that she did not have "evidence of prior infection, which could trigger transverse myelitis." *Id.* at 38. Dr. Höke testified that Petitioner's symptoms and imaging studies were consistent with TM, so "there [was] really nothing else in the differential diagnosis." *Id.* Dr. Höke explained that Petitioner had an "aberrant response" to the Hep B vaccine, which he "suspect[s] [was due to] a combination of [Petitioner's] genetic makeup or other risk factors." *Id.* at 32.

Dr. Höke testified that Petitioner is "the appropriate gender and age group," and that Petitioner's age group and gender "put[] her at high risk." Tr. 38, 44-45. He further testified that Petitioner had a vaccination which "case reports have shown [creates] an increased risk." *Id.* at 44-45. Therefore, in summary, Dr. Höke testified that Petitioner developed TM after receiving the Hep B vaccination because she was the "appropriate gender [and] age group, [had a] lack of any other risk factors, and [was] vaccinat[ed] with a vaccine that is known to be associated with . . . MS, which is a related disorder to [TM]." *Id.* at 60. Dr. Höke conceded that, if Petitioner had not received the Hep B vaccine, he would characterize her TM as idiopathic. *Id.* at 61. Dr. Höke acknowledged that none of Petitioner's treating physicians documented that they thought the Hep B vaccine may have caused Petitioner's TM. *Id.* at 48. However, Dr. Höke opined that "it really does [not] surprise [him]," because "a lot of physicians are not even aware of the adverse reporting system." *Id.* Thus, he testified that he believes it is more likely than not that the Hep B vaccine can cause a demyelinating disorder, and that it caused TM in Petitioner's case. *Id.* at 44, 45.

Dr. Höke testified that Petitioner's development of weakness and numbness while at work on June 24, 2013 "are the classical signs" of TM. Tr. 41. He opined that "the demyelination probably matured enough to cause the weakness around the day when she was admitted to the hospital." *Id.* Dr. Höke also discussed Petitioner's report of sensory symptoms, including "fatigue and some vague numbness [and] tingling" five days before her initial hospitalization. *Id.* He opined that "[i]t's possible" that those symptoms were the initial indications of her illness. *Id.* He explained that patients with TM often describe sensory symptoms, and that "fatigue is also a relatively common symptom that patients describe." *Id.* Dr. Höke noted that patients often "just don't feel like themselves and sometimes they can't even pinpoint it." *Id.* He contrasted a demyelinating illness like TM with a "very acute event" such as a stroke, where a patient develops symptoms immediately. *Id.* at 42. Dr. Höke explained that it "take[s] some time for the initial insult to start and for the inflammation to mature and cause significant demyelination to result in the weakness." *Id.* Therefore, Dr. Höke testified that the disease process began "probably somewhere around the time when she started to experience the tingling and numbness . . . five days before she had the paralysis." *Id.* Consequently, Dr. Höke opined that Petitioner's TM began sixty-two days after the administration of the Hep B vaccine, or June 19, 2013. *Id.* at 42-43. Dr. Höke acknowledged that "we don't know what the levels [of antibodies] are in her blood specifically." *Id.* at 60. However, "based on the published data, there's going to be very similar levels of antibodies in her blood at six weeks, eight weeks[,] or ten weeks" post-vaccination. *Id.* at 61. Dr. Höke testified that, given the medical literature and his testimony that antibody levels

do not sharply drop off on a particular date, he believes that the timing of Petitioner's symptom onset is medically appropriate to attribute her development of TM to the Hep B vaccine. *Id.* at 43.

Dr. Höke testified that he does not attribute any significance to the fact that the vaccine Petitioner alleges caused her TM was the third Hep B vaccine she received. Tr. 46. He testified that he is "not aware of any data to suggest that there [is] actually an increased risk for . . . [an] autoimmune process . . . after repeated challenges." *Id.* at 47. Dr. Höke also referenced a "very famous case from Australia," the authors of which he could not recall, about the influenza vaccine and its relationship with GBS. *Id.* at 48. He explained that the subject of that study received the influenza vaccine on three occasions over twelve years. *Id.* After each administration, the man suffered from GBS. *Id.* However, Dr. Höke testified that he did not remember whether the second or third reactions "happened faster after the vaccinations" than the first. *Id.*

B. Respondent's Expert, Timothy Vartanian, M.D., Ph.D

Dr. Timothy Vartanian ("Dr. Vartanian") authored one expert report in this case and testified at the hearing. Resp't Ex. A; Tr. 70-152. Dr. Vartanian is currently an attending neurologist at New York Hospital and a professor at Weill Cornell Medical College. Resp't Ex. B at 2; Tr. 70-71. He is board certified in neurology. Resp't Ex. A at 1; Tr. 72.

Dr. Vartanian estimated that eighty percent of his time is spent on research. Tr. 72. He testified that his recent research includes studying how demyelinating lesions initially form in the central nervous system. *Id.* at 73. That research includes researching infectious causes of lesion genesis, as well as how immunity causes demyelination in the central nervous system. *Id.* The research also includes studying treatments that will promote regeneration. *Id.* at 73-74.

Dr. Vartanian testified that his "clinical effort is technically around 10 percent [of his time], but that varies depending on . . . patient load and severity of cases." Tr. 72. Dr. Vartanian testified that the patients he sees are "[a]lmost exclusively multiple sclerosis, neuromyelitis optica . . . and transverse myelitis" patients, or patients coming for second or third opinions from other facilities. *Id.* at 73.

Dr. Vartanian stated that five percent of his time is spent teaching, and the remaining five percent is spent on administrative tasks. Tr. 72.

Dr. Vartanian testified that he has authored approximately fifteen expert reports in the Vaccine Program and has testified on one occasion. Tr. 74-75. He stated that his work in the Program has been exclusively for the Department of Health and Human Services. *Id.* at 75. Dr. Vartanian was accepted as an expert witness in the field of neurology and demyelinating diseases. *Id.*

i. Dr. Vartanian's Report

Dr. Vartanian authored his report on February 8, 2016. Resp't Ex. A. Dr. Vartanian noted that Petitioner received Hep B vaccinations on October 15, 2012 and April 18, 2013.[28] *Id.* at 2. He wrote that he "agree[s] with the diagnosis of acute [TM]" based on his "review of the clinical presentation, neurologic exams, and the neuroimaging." *Id.* Dr. Vartanian explained that Petitioner "developed weakness in her legs and what sounds like a fairly obvious sensory level" on June 24, 2013, but "[u]nfortunately, the diagnosis was missed." *Id.* He noted that she was diagnosed with TM on July 10, 2013. *Id.* He opined that the "unfortunate delay in diagnosis . . . translated into a delay of timely treatment," which "likely contributed to the persistence and severity of symptoms." *Id.*

Dr. Vartanian described his concerns with the case reports relied upon by Dr. Höke in his theory. Resp't Ex. A at 2. Dr. Vartanian wrote that case reports are intended "to make the community aware of **potential** risks." *Id.* at 3 (bold in original). He noted that "case reports are not proof of causality because they are not designed to be unbiased and they are certainly not statistically powered." *Id.* Dr. Vartanian wrote that the Agmon-Levin paper, Petitioner Exhibit 30, "does not achieve the minimal standards in epidemiology and bio-statistics to draw an inference." *Id.* He noted that the Agmon-Levin paper "is an aggregate of case studies and is [only] as strong as its weakest link." *Id.* Dr. Vartanian opined that the paper's "weakest link" is "essentially all of the case reports within it." *Id.* He explained that the authors of the Agmon-Levin paper drew conclusions from "a complex data set that involves[,] at a minimum[,] the following variables: incidence of [TM;] the frequency of each of the relevant vaccines[;] time from vaccination to symptoms[;] the presence or absence of infection clinically and documented by acute and convalescent titers for IgM and IgG for relevant organisms[; and] seasonal variation." *Id.* at 2-3. Dr. Vartanian emphasized that the Agmon-Levin paper "does not even provide a statistical framework to address such questions and thus is really more of a discussion of the literature[; it is] a medical hypothesis rather than an analysis of risk." *Id.* at 3. Dr. Vartanian also described the Karaali-Savrun paper, Petitioner Exhibit 36, as "simply a report of cases and a hypothesis." *Id.*

Additionally, Dr. Vartanian noted that the Agmon-Levin paper contains "no statistical analysis discerning the probability of chance occurrence versus potentially causal occurrence." Resp't Ex. A at 3. Dr. Vartanian explained that there are about 1,400 new cases of TM diagnosed each year in the United States.[29] *Id.* at 2. Therefore, he explained that, over a thirty-nine year span such as the period covered by the Agmon-Levin paper,[30] "the cumulative number of [TM] cases

[28] It is unclear whether Dr. Vartanian knew that Petitioner also received a Hep B vaccine in November 2012 at the time he authored his expert report.

[29] Dr. Vartanian attributes this statistic to the National Institute of Neurological Disorders and Stroke. *Transverse Myelitis Fact Sheet*, NAT'L INST. OF NEUROLOGICAL DISORDERS AND STROKE, http://www.ninds.nih.gov/disorders/transversemyelitis/detail_transversemyelitis.htm.

[30] Pet'r Ex. 30 at 1 (noting that the authors of the study reviewed journals published between 1970 and 2009).

would be an estimated 54,600." *Id.* at 2. He notes that the authors of the Agmon-Levin paper found only thirteen cases of TM which they associated with Hep B over that period of time. *Id.* Dr. Vartanian contrasted the Agmon-Levin paper with a paper authored by Shaw, et al., filed as Respondent Exhibit C. *Id.* at 3. He described the Shaw paper as an "expertly conducted study examining complications after the [H]ep[] B vaccine." *Id.* He notes that the authors in that study "ask[ed] the essential question: what is the expected rate of occurrence of transverse myelitis following vaccination and what is the observed rate[?]" *Id.* Dr. Vartanian explained that "[i]f the observed rate [of occurrence] is greater than the expected rate [of occurrence], then a signal exists and warrants further investigation." *Id.* However, he noted that the authors of the Shaw paper found that "the observed rate of [TM] following vaccination was the same or lower than the expected rate." *Id.* Dr. Vartanian wrote that "[c]ausality is the job of epidemiologists and public health scientists, and when they have investigated this question, the risk observed is not greater than the risk expected." *Id.*

Dr. Vartanian wrote that TM "is a demyelinating disease of the Central Nervous System" ("CNS"). *Id.* at 4. He explained that TM "often occurs as a presenting symptom of [MS] [or] Neuromyelitis optica, [but that it] may remain as an isolated spinal cord disease." *Id.* Dr. Vartanian explained that because MS is a more common disease, "much of what we know about environmental exposures comes from the MS literature and is extrapolated to TM." *Id.* He noted that "MS and TM share many pathophysiologic steps." *Id.* He explained that "[p]art of th[e] difficulty in ascribing pathophysiologic mechanisms to TM is that the number of cases with comprehensive histopathologic assessments reported in the literature are few[,] and the clinical presentation is quite variable." *Id.* Dr. Vartanian wrote that "the data associating prior infection as a risk factor for TM is reasonably strong[,] whereas the data associating prior vaccination with TM remains extraordinarily weak and circumstantial." *Id.* at 4.

Dr. Vartanian wrote that the National Multiple Sclerosis Society ("NMSS") has conducted "extensive review" on "the relationship between vaccine[s] and CNS demyelinating disease." *Id.* at 4. He then provided five excerpted paragraphs from a document on the NMSS website,[31] without commenting on any of the excerpts. *Id.* Each of the excerpts from the NMSS website reflects that different organizations and studies have found no association between vaccines (including the Hep B vaccine) and MS, optic neuritis, and/or "any other acquired central nervous system demyelinating disease." *Id.*

Dr. Vartanian wrote that "[t]he cause of TM, like that of MS, is unknown, but autoimmunity is thought to play a role." *Id.* at 3. However, Dr. Vartanian wrote that "[w]e know that peak antibody responses after hepatitis B immunization occur[s] around week 2." *Id.* at 4. As an example, he quoted the Sam paper, which states that "[t]he mean titer of anti-HBs antibody at week 2 after booster vaccination was higher than at other time intervals." *Id.* (quoting Resp't Ex. H at 4). Dr. Vartanian wrote that "[i]n cases where there has been a causal link between immunization and human disease[,] the onset of symptoms is typically within 2-4 weeks [after]

[31] *Living Well With MS: Diet, Exercise & Healthy Behaviors—Vaccinations,* NAT'L MULTIPLE SCLEROSIS SOC'Y, https://www.nationalmssociety.org/Living-Well-With-MS/Diet-Exercise-Healthy-Behaviors/Vaccinations.

the immunization." *Id.* at 5. Dr. Vartanian wrote that the onset of Petitioner's symptoms, which he states occurred on June 20, 2013, was 63 days after her last Hep B vaccination. *Id.* at 4. He opined that "63 days is far too long for molecular mimicry to be implicated." *Id.*

In summary, Dr. Vartanian wrote that "Dr. Höke's review of [TM] and the facts of this case are accurate, but his connection between [H]ep[] B vaccination and the cause or risk of [TM] in this case is not substantiated." Resp't Ex. A at 5. He opined that "[t]he medical literature and evidence here does not support a causal relationship between [TM] and [H]ep[] B vaccination." *Id.*

ii. Dr. Vartanian's Testimony

Dr. Vartanian testified that Dr. Höke's testimonial description of TM was "perfectly adequate." Tr. 77. Dr. Vartanian testified that he "[a]bsolutely" agrees with Petitioner's diagnosis of TM. *Id.* at 105-06. Dr. Vartanian testified that, based on Petitioner's medical records, her symptoms of TM began on June 24, 2013. *Id.* at 77. He testified that he did not recall seeing earlier symptoms, including fatigue and facial numbness, described in her medical record. *Id.* Regardless, Dr. Vartanian testified that the location of the lesion in Petitioner's thoracic spine would not have caused facial numbness.[32] *Id.* at 77-78. Dr. Vartanian testified that Petitioner "ha[d] a fairly classic presentation" of TM, and noted that Petitioner "had a big lesion." *Id.* at 102-03. Dr. Vartanian opined that the onset of Petitioner's symptoms was "a little atypical" because "it was very rapid." *Id.* at 92. He explained that TM typically presents, "from first symptoms to maximum," over "a day or a couple days." *Id.* at 93. Dr. Vartanian testified that the severity of Petitioner's TM "was monumental." *Id.* He also noted that there was a delay in arriving at her diagnosis, "[s]o she never received proper treatment for her disease." *Id.*

Dr. Vartanian agreed with Dr. Höke that demyelinating disorders such as TM are most common in people between the ages of 20 and 40. Tr. 108. Dr. Vartanian also agreed that the current data shows that women are between 1.5 and 3 times more likely than men to be at risk for MS. *Id.* at 107. Dr. Vartanian testified that "there [is] an increased risk of an exacerbation in MS" during the postpartum period in women, which is "the only pregnancy-related data that [he] know[s] of" relating to demyelinating disorders. *Id.* at 145. For TM specifically, Dr. Vartanian testified that "the data [on male-versus-female risk] is actually variable." *Id.* at 108. He explained that in some reports, the risk is equal for men and women, while in other reports TM is more common in women. *Id.* Dr. Vartanian emphasized that "[t]here aren't that many cases" of TM; "the incidence [of TM] is ten per million per year." *Id.*

Dr. Vartanian testified that "all inflammatory demyelinating diseases are thought to be immune-mediated." Tr. 106. Dr. Vartanian testified that a recent publication "points out that 30

[32] He explained that facial numbness may occur if a TM lesion is "in the very upper cervical spinal cord," but that was "not at all" what happened in Petitioner's case. Tr. 101.

to 60 percent of [TM cases] seem[] to follow an antecedent infection."[33] *Id.* at 93. He noted that the percentages are analogous to GBS. *Id.* Additionally, Dr. Vartanian testified that a patient does not "have to have a clinical infection to have a microorganism be responsible for the illness." *Id.* at 95. To illustrate his point, Dr. Vartanian stated that "it [has] been recently shown" that when patients with GBS are tested "using a more sensitive assay for Campylobacter,[34] then the number of people who . . . are positive for Campylobacter approaches 70 or 80 percent," even though "from a gastrointestinal point of view, they are asymptomatic." *Id.* at 94-95. In contrast, Dr. Vartanian explained that, "in a healthy control population, th[at] number is 3 percent." *Id.* at 95.

Dr. Vartanian testified that he believes "that immunization with . . . an antigen can lead to molecular mimicry," which can cause an autoimmune reaction. Tr. 106. Thus, Dr. Vartanian agreed with Petitioner's counsel that "it's possible that immunization could trigger a molecular mimicry cross-reaction that would entail autoimmunity leading to transverse myelitis." *Id.* However, Dr. Vartanian also testified that "anything is possible under some really complex and unusual circumstance." *Id.* at 129. Dr. Vartanian testified that he does not believe "there is remotely sufficient data for us to say [whether] molecular mimicry is a reasonable mechanism by which [H]ep[] B can cause central nervous system demyelination." *Id.* at 85. Dr. Vartanian acknowledged "from the outset" that he is "not an epidemiologist," but he testified that "the epidemiological data is simply not there" to support the Petitioner's theory. *Id.* Dr. Vartanian testified that "epidemiology is an extraordinar[ily] difficult science because there are so many variables." *Id.* at 135. He explained that "data sets are cumbersome," and there are "problems with reliability on so many levels." *Id.*

Dr. Vartanian discussed several papers which looked at a possible association between vaccines and TM. Dr. Vartanian acknowledged that, in a 2011 article, authors Awad and Stüve wrote that thirty percent of pediatric TM cases are preceded by immunization within one month. Tr. 109; Pet'r Ex. 33 at 3. However, he testified that he does not agree with that statement, and that he has not "seen anything to support that" association, other than the statement in the Awad and Stüve article, which references "one very, very old paper" and a case report with nine cases. Tr. 110. Therefore, Dr. Vartanian testified that he does not "know of any association" between vaccines and TM in the pediatric population.[35] *Id.* at 111.

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[33] The referenced publication was not specifically identified or filed. However, Dr. Vartanian testified that it was authored by Doug Kerr, who he believes founded the Transverse Myelitis Center at Johns Hopkins. Tr. 93.

[34] Dr. Vartanian explained that GBS is known to be caused by an immune response to "complex carbohydrates on the surface of Campylobacter jejuni." Tr. 94. He stated that Campylobacter "is the most common organism" found where there is a known antecedent gastrointestinal infection in a patient who has developed GBS. *Id.*

[35] Petitioner received all of her Hep B vaccines while she was in her early twenties, so she would not be considered a pediatric patient. However, Dr. Vartanian acknowledged that there is "something different about a 22 year old [and] a 40 year old in terms of their brain[s]," and agreed with Petitioner's counsel's statement that "the sharp distinction between pediatric and adult doesn't exist in nature." Tr. 112-13. Dr. Vartanian stated that he does not know of any data as to

Discussing studies that looked at cases of TM following vaccination in the general population, Dr. Vartanian testified that the 2016 Baxter paper "is a significantly better study" than the 1988 Shaw paper. Tr. 98. In the Shaw paper, the authors found four cases of TM among 850,000 people who received the Hep B vaccine.[36] *Id.*; Resp't Ex. C. In contrast, in the Baxter study, which involved "[o]ver nine million subjects in the cohort and over 64 million vaccines" administered between 2007 and 2013, the authors found "only two patients [who] developed [TM] as a first ever event" after receiving the Hep B vaccine.[37] Tr. 95, 98-99; Resp't Ex. L. Dr. Vartanian agreed with Dr. Höke's assessment that reporting of adverse events is "not as good as we want it to be." Tr. 98. However, Dr. Vartanian testified that the Baxter paper "is, by far, the best" of the papers that he looked at because "the [sample size] is the largest and the analysis is really well done." *Id.* at 138. He explained that, because the authors of that paper collected data by reviewing medical records and identifying the diagnostic codes used by the treating physicians themselves, that study was "less subject to underreporting than a typical study." *Id.* at 99, 138.

Dr. Vartanian acknowledged that TM in general, and vaccine reactions in general, are rare. Tr. 150. With the disclaimer that he is not an epidemiologist, Dr. Vartanian testified that such rare events can be properly accounted for with epidemiological studies "if the studies are large enough." *Id.* at 150-51. Dr. Vartanian testified that the relative rarity of TM generally does not affect his view of the accuracy of the results in the Baxter study, as he believes the Baxter study was sufficiently large to account for the rarity of both TM and vaccine reactions. *Id.* at 140, 150-51. In fact, he testified that, "by virtue of the fact that they had so few cases [of TM] and so many vaccines, it really hammers home the point that the vaccine is probably not related" to TM. *Id.* at 141.

Dr. Vartanian noted that the 2004 Hernán paper is the only study he has seen where there was an association found between the Hep B vaccine and TM. Tr. 99. Discussing that paper, Dr. Vartanian explained that the methodology used represents "a very legitimate way of doing a study." *Id.* at 85-86; Pet'r Ex. 58. Dr. Vartanian testified that the paper is "[a]bsolutely not" perfect, but that it is "better than the case reports."[38] Tr. 135. However, Dr. Vartanian explained

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whether the difference in a 22-year-old's brain and a 40-year-old's brain potentially makes one more susceptible to autoimmunity following a vaccination. *Id.* at 112.

[36] Dr. Vartanian acknowledged that the Shaw paper analyzed reports of neurological illness following administration of a plasma-derived Hep B vaccine, whereas the Hep B vaccine currently in use is the recombinant Hep B vaccine. Tr. 136; Resp't Ex. C. Dr. Vartanian testified that the two vaccines do not create an "optimal comparison," but that he "would imagine the risk would have been worse" with the plasma-derived vaccine, because "it's probably not as good of a vaccine in terms of its cleanliness." Tr. 137.

[37] Among all of the recipients of any vaccine, the authors found seven cases of TM. Tr. 99.

[38] Dr. Vartanian described the Agmon-Levin paper, Petitioner Exhibit 30, as a series of case reports and a review of the literature. Tr. 89. Dr. Vartanian testified that the Karaali-Savrun paper, Petitioner Exhibit 36, is likewise "just case reports." *Id.*

that the 2004 Hernán paper "disagrees with the prior studies," and was "a direct contradiction to another major study" done previously by DeStefano. *Id.* at 86, 88; Resp't Ex. M.[39] Dr. Vartanian testified that the authors of the 2004 Hernán paper acknowledged some of its shortcomings, and he noted that the medical community did not know about "other risk factors for MS that could . . . be confounders" for the disease, such as occupation, vitamin D, and smoking. Tr. 87. Dr. Vartanian testified that the 2004 Hernán paper prompted DeStefano to review the methodology and reanalyze the data set. *Id.* at 88. He testified that, after reanalysis, DeStefano and his coauthors "didn't come up with an association between MS and the hepatitis B vaccine." *Id.*; Resp't Ex. N.[40] Thus, while the 2004 Hernán paper found an increased risk of MS after Hep B vaccination, Dr. Vartanian testified that the balance of the medical literature, including the 2006 Hernán paper, supports no such risk. Tr. 88; Resp't Ex. J.

Dr. Vartanian testified that the 2006 Hernán paper "reminded [him] of academic arguing, like intellectual banter." Tr. 151. He explained that "DeStefano had done very important work in 2002. Hernán refuted that in 2004. DeStefano reanalyzed the data sets based on Hernán 2004 and still . . . didn't come up with an association." *Id.* Therefore, Dr. Vartanian testified that he "felt like Hernán was trying to justify their original study in some way and explain the differences," and Dr. Vartanian thought "[t]hey did the best that they could at that." *Id.* at 151-52. He testified that "[t]he problem in all cases is that" the authors were not working with the same data set for all three studies, and the epidemiology itself is complicated. *Id.* at 152.

Based on his analysis of the literature, Dr. Vartanian testified that "there is no statistical association" between the Hep B vaccine and TM. Tr. 99. He also noted that he did not see an indication in the medical records that any of Petitioner's treating physicians believed that her third Hep B vaccine played a role in the development of TM. *Id.* at 100.

Dr. Vartanian also testified regarding Petitioner's molecular mimicry theory of causation. Preliminarily, Dr. Vartanian testified that there is "no data that you need an injury . . . to the blood-brain barrier outside of the immune response to get . . . focal or multifocal inflammatory [central nervous system] demyelination." Tr. 100. Dr. Vartanian testified that he does not know of "any data from what we know about autoimmunity [or] molecular mimicry that requires a secondary event for central nervous system demyelination." *Id.* at 149. As an example, he testified that the original rabies vaccines "had a very high incidence of inducing acute disseminated encephalomyelitis." *Id.* He explained that the rabies vaccine is "a human example . . . in which

[39] Frank DeStefano, Thomas Verstraeten, Lisa A. Jackson, Catherine A. Okoro, Patti Benson, Steven B. Black, Henry R. Shinefield, John P. Mullooly, William Likosky & Robert T. Chen, *Vaccines and Risk of Central Nervous System Demyelinating Diseases in Adults*, 60 ARCHIVES NEUROLOGY 504 (2003).

[40] Frank DeStefano, Eric S. Weintraub & Robert T. Chen, *Correspondence to the Editor*, 64 NEUROLOGY 1317 (2005) (letter to the editor regarding Miguel A. Hernán, Susan S. Jick, Michael J. Olek & Hershel Jick, *Recombinant Hepatitis B Vaccine and the Risk of Multiple Sclerosis: A Prospective Study*, 63 NEUROLOGY 838 (2004)).

peripheral immunization, without anything else going on, cause[d] a central nervous system disease without a second hit or second event." *Id.* at 149-50.

Dr. Vartanian explained that, related to "molecular mimicry, the [amount of] basic scientific literature is enormous for central nervous system demyelination." Tr. 82. He testified that there are "over 12,000 articles published" for just one animal model, experimental allergic encephalomyelitis ("EAE").[41] *Id.* at 82-83. In contrast, there are "relatively few[,] . . . maybe less than 1,000[,] articles on the peripheral nervous system equivalent to that model." *Id.* at 82. During his testimony, Dr. Vartanian drew a graph of disease progression in the EAE model. Resp't Ex. K (bottom graph). He explained that after a healthy animal is immunized with any myelin antigen, they progressively start to get sick, "they have peak disease" by two to three weeks, and then the severity of the disease progressively lessens. Tr. 83. Thus, the EAE model shows a bell-shaped curve, with the top of the curve occurring around two or three weeks post-immunization. Resp't Ex. K (bottom graph). Dr. Vartanian emphasized that the chart's bell-shaped curve is "not an incidence curve" representing the "frequency of disease onset." Tr. 124. Instead, it is a "disease severity curve." *Id.* Therefore, he explained, it is "very reliable" that the onset of disease will cluster at or near the peak of the bell-curve.[42] *Id.*

Dr. Vartanian testified that "molecular mimicry, as we understand it scientifically, [ ] typically follows the peak immune response . . . fairly closely." Tr. 118. He explained that, based on "the data for the immune response, as we understand molecular mimicry from a humoral standpoint, [ ] that peak happens [at] two to three weeks." *Id.* at 129. Dr. Vartanian, referencing Respondent Exhibit H, testified that peak immune response to the Hep B vaccine, and vaccines generally, is "around two weeks."[43] *Id.* at 91. He noted that immune response can be represented

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[41] EAE is "an animal model for acute disseminating encephalomyelitis in which the characteristic pathophysiology and clinical signs of this disease are produced by immunization of an animal with extracts of brain tissue or with myelin basic protein together with Freund adjuvant; it is transferable by adoptive transfer of lymphocytes but not by serum." *Dorland's Illustrated Medical Dictionary* 614 (32nd ed. 2012) [hereinafter "*Dorland's*"].

[42] Dr. Vartanian acknowledged that "[t]he human nervous system is more complex than a monkey or a mouse." Tr. 125. Dr. Vartanian thus agreed with Petitioner's counsel that "there are reasons to be cautious about extrapolation from animal models to conclusions about . . . medical theories in general in humans." *Id.* at 126. However, he testified that approximately "90 percent of the autoimmunity animal modeling for MS or allied diseases is done in rodents." *Id.* at 125. He noted that the original studies were conducted with monkeys, and that there are still some studies with primates, but "the data for that is . . . very much similar to the rodent work." *Id.* at 125.

[43] Dr. Vartanian acknowledged that the literature provides varying timelines for peak response to vaccines. Tr. 113-15. However, he testified that there is a lot of variation in the response to different vaccines, and he opined that "if [he] were going to make a comment on when [ ] the humoral response peak[s] following a [H]ep[] B vaccine, [he] would go to hepatitis B literature." *Id.* at 115. Dr. Vartanian testified that the Hep B literature that he is familiar with places peak response at "mostly around two weeks." *Id.*

by "a bell-shaped curve, but it really peaks around two weeks." *Id.* He also testified that "there [is] a lot of other data out there that supports this timing of peak immune response." *Id.* He testified that he could "come up with a list of . . . probably 15 or 20 papers that all show this timing for the peak immune response being two to three weeks after immunization." *Id.* After peak immune response, he explained, the process of molecular mimicry "follows relatively quickly," based on "what we know about immunity and secondary injury to the nervous system." *Id.* at 129.

Dr. Vartanian explained that the reason three Hep B vaccinations are given is so that the recipient gets a "big boost in antibody titers." Tr. 79. Dr. Vartanian testified that with the first and second vaccinations, "there is a big increase in the number of B cells that are specific to the surface antigen for hepatitis B in the vaccine[, b]ut the immune response is not that big." *Id.* He explained that, in contrast, "the immune response with a booster is really robust." *Id.* Dr. Vartanian testified that one should not "us[e] the B cells as a measure of what [ ] the pathogenic response is." *Id.* at 131-32. Instead, one should look at "the humoral response, which is the serum antibody levels." *Id.* at 132.

Dr. Vartanian drew a graph to illustrate the immune system's B-cell response after the first, second, and third Hep B vaccinations. Resp't Ex. K. He illustrated that "the percentage of circulating B cells, which are the antibody-producing cells that are the memory cells," rises quickly after the first vaccination. Tr. 81; Resp't Ex. K (dotted line in top chart). The number of B-cells then drops, but the cells are still above baseline by the second vaccination. *Id.* After the second vaccination, the number of B-cells "go[es] up a little" again, but does not reach the same peak as after the first vaccination. *Id.* After the third vaccination, the number of B-cells "go[es] up even less." *Id.* Thus, Dr. Vartanian explained that "the cells that are making the antibod[ies] are really induced early on," which creates "immunologic memory or central memory." Tr. 81.

Dr. Vartanian also explained and graphed typical antibody response, specifically the Immunoglobulin-G ("IgG")[44] response.[45] Tr. 81-82; Resp't Ex. K (solid line in top chart). He illustrated that IgG levels rise slightly in response to the first and second vaccinations, lowering again between vaccinations but remaining above baseline. *Id.* In contrast, after the third vaccination, the response "just goes way up." *Id.* He explained that "there [is a] massive increase in the number of circulating antibodies" after the third vaccination. Tr. 82. Dr. Vartanian explained that the peak IgG response illustrated in his graph occurs two or three weeks after the third vaccination. Tr. 82; Resp't Ex. K (solid line in top chart). Based on that understanding, Dr. Vartanian testified that the fact that Petitioner had no apparent adverse response after the first two Hep V vaccinations is of no consequence, while he testified that it is significant that Petitioner's symptoms began after her third Hep B vaccination. Tr. 78-79, 147.

To further illustrate his explanation of the antibody response after vaccination, Dr. Vartanian referenced Table 1 of the Sam paper, Respondent Exhibit H. Tr. 133; Resp't Ex. H at

[44] "Immunoglobulin" refers to "any of the structurally related glycoproteins that function as antibodies, divided into five classes (IgM, IgG, IgA, IgD, and IgE) on the basis of structure and biologic activity." *Dorland's* at 919.

[45] He testified that there is "a similar but lesser pattern" for Immunoglobulin-M response. Tr. 82.

4. Dr. Vartanian noted that the table shows the anti-Hep B surface antigen antibodies in seven patients before and after booster vaccination. Tr. 133. Dr. Vartanian explained that the subjects' individual antibody levels varied widely when compared to each other both before vaccination (where known) and after vaccination. *Id.* However, Dr. Vartanian emphasized that, for each of the seven subjects, individual peak response came at week two. *Id.* Dr. Vartanian acknowledged that each of the individuals' antibody levels remained "much higher" than pre-vaccination levels at weeks 4, 8, and 16 post-vaccination. *Id.* at 134.

Dr. Vartanian testified that "for molecular mimicry in general, you have to have some minimum quantity [of] T cell or humoral immunity." Tr. 121. He explained that if a person is "susceptible to autoimmunity following an immunization," the question is "not what [that person's] minimal titer requirement is at some distant time point." *Id.* Instead, Dr. Vartanian explained that the question is when the person first achieves that minimal titer requirement for autoimmunity after immunization, "because at that point is when symptoms occur." *Id.* In other words, although a person's immune response may elevate, peak, and then lower but remain elevated above baseline for an extended period of time, an autoimmune response, if it is going to occur, would be expected to occur the first time autoimmune response reaches a particular level. Therefore, he testified that, despite a patient's antibody levels remaining higher than baseline for an extended period, "it's unlikely" that TM appearing at week eight after vaccination would be vaccine-related. *Id.* at 134-35.

Dr. Vartanian acknowledged that medicine is complex, and that "things don't present exactly the same in any two patients ever." Tr. 90. Dr. Vartanian explained that "the human body is complex, the immune system is complex, [and] the nervous system is complex." *Id.* at 115. Therefore, he admitted that when "the two most complex systems . . . interact to cause a disease, there [is] a lot of variation." *Id.* However, he testified that "when we come up with [ ] cutoffs for timing, the cutoff happens because we're trying to think, okay, what is our limit, what is the limit we would accept as rational for timing." *Id.* at 90. He explained that, "if we go beyond that rational limit, then 100 percent of anything that happens to anyone who gets vaccinated will always be legitimate." *Id.*

In Dr. Vartanian's opinion, any incident of autoimmunity at sixty days post-vaccination "is an outlier." Tr. 130. He testified that he does not "know who came up with that 60 days," but he "imagine[s] that [the 60-day time frame] came to be to make sure that we were capturing beyond -- beyond question most -- the majority of cases." *Id.* Therefore, Dr. Vartanian testified that Petitioner's onset of symptoms, even if it was 62 days after the vaccination, "medically does not fit and scientifically does not fit." *Id.* at 91-92. He testified that Petitioner's TM was idiopathic. *Id.* at 92.

IV. The Applicable Legal Standard

To receive compensation under the Vaccine Act, Petitioner must demonstrate either that: (1) Petitioner suffered a "Table injury" by receiving a covered vaccine and subsequently developing a listed injury within the time frame prescribed by the Vaccine Injury Table set forth at 42 U.S.C. § 300aa-14, as amended by 42 C.F.R. § 100.3; or (2) that she suffered an "off-Table injury," one not listed on the Table as a result of her receipt of a covered vaccine. *See* 42 U.S.C.

§§ 300aa-11(c)(1)(C); *Moberly v. Sec'y of Health & Human Servs.*, 592 F.3d 1315, 1321 (Fed. Cir. 2010); *Capizzano v. Sec'y of Health & Human Servs.*, 440 F.3d 1317, 1319-20 (Fed. Cir. 2006). Petitioner does not allege a Table injury in this case; thus she must prove that her injury was caused-in-fact by a Table vaccine.

To establish causation-in-fact, Petitioner must demonstrate by a preponderance of the evidence that the vaccine was the cause of the injury. 42 U.S.C. § 300aa-13(a)(1)(A). Petitioner is required to prove that the vaccine was "not only a but-for cause of the injury but also a substantial factor in bringing about the injury." *Moberly*, 592 F.3d at 1321-22 (*quoting Shyface v. Sec'y of Health & Human Servs.*, 165 F.3d 1344, 1352-53 (Fed. Cir. 1999)).

In the seminal case of *Althen v. Secretary of the Department of Health and Human Services*, the Federal Circuit set forth a three-pronged test used to determine whether a petitioner has established a causal link between a vaccine and the claimed injury. *See* 418 F.3d 1274, 1278-79 (Fed. Cir. 2005). The *Althen* test requires the petitioner to set forth: "(1) a medical theory causally connecting the vaccination and the injury; (2) a logical sequence of cause and effect showing that the vaccination was the reason for the injury; and (3) a showing of a proximate temporal relationship between vaccination and injury." *Id.* at 1278. To establish entitlement to compensation under the Program, Petitioner is required to establish each of the three prongs of *Althen* by a preponderance of the evidence. *See id.*

Specifically, under the first prong of *Althen*, Petitioner must offer a scientific or medical theory that answers in the affirmative the question "can the vaccine(s) at issue cause the type of injury alleged?" *See Pafford v. Sec'y of Health & Human Servs.*, No. 01-0165V, 2004 WL 1717359, at *4 (Fed. Cl. Spec. Mstr. July 16, 2004), *aff'd*, 64 Fed. Cl. 19 (2005), *aff'd*, 451 F.3d 1352 (Fed. Cir. 2006). To satisfy this prong, a petitioner's theory must be based on a "sound and reliable medical or scientific explanation." *Knudsen v. Sec'y of Health & Human Servs.*, 35 F.3d 543, 548 (Fed. Cir. 1994). Such a theory must only be "legally probable, not medically or scientifically certain." *Id.* at 548-49. This may be accomplished in a number of ways.

"Reliability and plausibility of [ ] pathogenesis can be bolstered by providing evidence that at least a sufficient minority in the medical community has accepted the theory as to render it credible." *Pafford*, 2004 WL 1717359, at *4. Additionally, "epidemiological studies and an expert's experience, while not dispositive, lend significant credence to the claim of plausibility." *Id.* "Articles published in respected medical journals, which have been subjected to peer review, are also persuasive."[46] *Id.*

[46] Both parties filed medical and scientific literature in this case, but not every filed item factors into the outcome of this decision. While the undersigned has reviewed all of the information filed in this case, only those articles and records that are most relevant to the decision will be discussed. *Moriarty v. Sec'y of Health & Human Servs.*, 844 F.3d 1322, 1328 (Fed. Cir. 2016) ("We generally presume that a special master considered the relevant record evidence even though he does not explicitly reference such evidence in his decision.") (citation omitted); *see also Paterek v. Sec'y of Health & Human Servs.*, 527 F. App'x 875, 884 (Fed. Cir. 2013) ("Finding certain information not relevant does not lead to–and likely undermines–the conclusion that it was not considered.").

However, publication of an article "'does *not* necessarily correlate with reliability,' because 'in some instances well-grounded but innovative theories will not have been published.'" *Id.* (*quoting Daubert v. Merrell Dow Pharmaceuticals, Inc.*, 509 U.S. 579, 593–94 (1993)) (emphasis in original). Therefore, petitioners may satisfy the first *Althen* prong without relying on medical literature, epidemiological studies, demonstration of a specific mechanism, or a generally accepted medical theory. *Andreu v. Sec'y of Health & Human Servs.*, 569 F.3d 1367, 1378-79 (Fed. Cir. 2009) (citing *Capizzano v. Sec'y of Health & Human Servs.*, 440 F.3d 1317, 1325-26 (Fed. Cir. 2006)). Special masters, despite their expertise, are not empowered by statute to conclusively resolve what are essentially thorny scientific and medical questions, and thus scientific evidence offered to establish *Althen* prong one is viewed "not through the lens of the laboratorian, but instead from the vantage point of the Vaccine Act's preponderant evidence standard." *Id.* at 1380. Accordingly, special masters must take care not to increase the burden placed on petitioners in offering a scientific theory linking vaccine to injury. *Contreras v. Sec'y of Health & Human Servs.*, 121 Fed. Cl. 230, 245 (2015) ("[p]lausibility . . . in many cases *may* be enough to satisfy *Althen* prong one" (emphasis in original)), *vacated on other grounds*, 844 F.3d 1363 (Fed. Cir. 2017). But this does not negate or reduce a petitioner's ultimate burden to establish his overall entitlement to damages by preponderant evidence. *W.C. v. Sec'y of Health & Human Servs.*, 704 F.3d 1352, 1356 (Fed. Cir. 2013) (citations omitted).

In addition to showing that the vaccine at issue can cause a particular injury, a petitioner must also, under *Althen's* second prong, prove that the vaccine actually did cause the alleged injury in a particular case. *See Pafford*, 2004 WL 1717359, at *4; *Althen*, 418 F.3d at 1279. The second *Althen* prong requires proof of a logical sequence of cause and effect, usually supported by facts derived from a petitioner's medical records. *Althen*, 418 F.3d at 1278; *Andreu*, 569 F.3d at 1380; *Capizzano*, 440 F.3d at 1326; *Grant v. Sec'y of Health & Health Servs.,* 956 F.2d 1144, 1148 (Fed. Cir. 1992). Medical records are generally viewed as particularly trustworthy evidence, since they are created contemporaneously with the treatment of the patient. *Cucuras v. Sec'y of Health & Human Servs.*, 993 F.2d 1525, 1528 (Fed. Cir. 1993). A petitioner does not meet this obligation by showing only a temporal association between the vaccination and the injury; instead, the petitioner "must explain *how* and *why* the injury occurred." *Pafford*, 2004 WL 1717359, at *4 (emphasis in original).

While a temporal association alone is insufficient to establish causation, under the third prong of *Althen*, a petitioner must show that the timing of the injury fits with the causal theory. *See Althen*, 418 F.3d at 1278. For example, if the petitioner's theory involves a process that takes several days to develop after vaccination, an injury that occurred within a day of vaccination would not be temporally consistent with that theory. Conversely, if the theory is one that anticipates a rapid development of a reaction post-vaccination, the development of the alleged injury weeks or months post-vaccination would not be consistent with that theory. Causation-in-fact cannot be inferred from temporal proximity alone. *See Grant v. Sec'y of Health & Human Servs.*, 956 F.2d at 1148; *Thibaudeau v. Sec'y of Health & Human Servs.*, 24 Cl. Ct. 400, 403-04 (1991); *see also Hasler v. United States*, 718 F.2d 202, 205 (6th Cir. 1983) ("Without more, [a] proximate temporal relationship will not support a finding of causation.").

A petitioner who demonstrates by a preponderance of the evidence that she suffered an injury caused by vaccination is entitled to compensation, unless Respondent can demonstrate by a

preponderance of the evidence that the injury was caused by factors unrelated to the vaccination. *See Althen*, 418 F.3d at 1278; *Knudsen*, 35 F.3d at 547.

V. Discussion

A. Experts

In this case, the experts presented by Petitioner and Respondent agree on Petitioner's diagnosis of acute TM. Dr. Höke and Dr. Vartanian are both neurologists who focus on research and academia, but also maintain a small practice area that includes patients with TM. Dr. Höke's expertise is rooted in research specific to peripheral neuropathy, while Dr. Vartanian focuses on the central nervous system and incorporates an immunology component into his research. As a result, Dr. Höke is less conversant on the timing and nature of the immunological pathogenesis of TM, and his theory is vague in that area. Dr. Vartanian's experience in immunology research allows him to effectively distinguish between diseases that attack the central and peripheral nervous systems, and to further explain how although molecular mimicry may be a plausible mechanism for vaccine injury in other circumstances, it is not applicable in this case.

B. *Althen* Prong One

Petitioner's theory is based on the concept of molecular mimicry, which has been proffered successfully in several cases involving demyelinating conditions, including TM. *Schmidt v. Sec'y of Health & Human Servs.*, No. 07-20V, 2009 WL 5196169 (Fed. Cl. Spec. Mstr. Dec. 17, 2009); *Hargrove v. Sec'y of Health & Human Servs.,* No. 05-0694V, 2009 WL 1220986 (Fed. Cl. Spec. Mstr. Apr. 14, 2009). Furthermore, the recent addition of GBS to the list of vaccine table injuries provides evidence that Respondent does not deny outright that at least one demyelinating condition, albeit one that affects the peripheral nervous system, can be caused by vaccination.[47]

In his reports and during his testimony, Dr. Höke relied heavily on papers that discuss vaccine-related GBS. Dr. Höke described GBS as "the most well-studied experimentally of all autoimmune diseases of the nervous system," and stated that "the molecular mimicry process was really well proven" because the medical community has identified how a particular antibody "makes a mistake and goes and attacks a corresponding molecule on the nervous tissue." Tr. 63. Dr. Höke analogizes this reaction to TM, stating that although the conditions affect different branches of the nervous system, "there is a similar process" but we "just don't know what the protein is or lipid is or sugar moiety is." *Id.* Despite Dr. Höke's inability to provide any support for his contention that the causation theory that has been used to explain the development of GBS following the administration of some vaccines should be applied to TM following the Hep B vaccine, it certainly seems plausible that there may be an avenue by which molecular mimicry serves as the catalyst for inflammation and neurological injury. Indeed, Dr. Vartanian admitted that he believes that "immunization with . . . an antigen can lead to molecular mimicry." *Id.* at 106.

[47] GBS occurring after receipt of a seasonal flu vaccine, with the first symptom occurring not less than 3 days and not more than 42 days post-vaccination, is a Table injury. 42 C.F.R. § 100.3(a)(XIV)(D).

The strength of the theory used to explain how GBS occurs as the result of vaccination lies in the fact that it is so widely studied and understood. Without a similar understanding of TM, or an explanation of why the two conditions would be synonymous in pathogenesis, the diseases are not simply interchangeable within a causation theory. The Vaccine Act, pursuant to the preponderance standard, does not require identification and proof of specific biological mechanisms. *Althen*, 418 F.3d at 1280 (quoting *Knudsen*, 35 F.3d at 549). In fact, the very nature of a program anticipates that vaccine injury is a "field bereft of complete and direct proof of how vaccines affect the human body." *Id.* It is not enough, however, to find a theory that has been successful in the past and insert it into a case involving a similar condition without a plausible explanation of why the theory continues to work.

Dr. Höke provided a brief overview of two papers that included case reports of patients presenting with TM following a Hep B vaccination. Pet'r Exs. 30, 36. He then discussed the Hernán paper, which had a larger patient pool but focused on MS following a Hep B vaccination. Pet'r Ex. 58. Dr. Höke used the Hernán paper to point out that there was an increase in the number of MS patients that were vaccinated against Hep B for 3 years following vaccination. Tr. 35. Dr. Höke continued that for these patients, the antibodies that developed in their systems following vaccination remained high. *Id.* at 36. He also noted that in another study, "the levels of the antibody response among patients who received Hep B vaccine" showed "no statistically significant differences between week 8 and 16." *Id.*; Resp't Ex. H. At that point in his testimony, Dr. Höke did not immediately explain why these sustained elevated antibody titers were important to his theory. Instead, he made a general assertion that the Hernán paper "clearly shows that there was a threefold higher incidence of MS in patients who received [a] [H]ep B vaccine," which "shows a possible link between an event and a certain disease." Tr. 40. He continued that, despite his discussion of scientific literature, the research "may not be that easy to use . . . because there are so many other variables that may not be obvious in an epidemiological study." *Id.* Dr. Höke mentioned a pre-existing susceptibility or "inflammatory response or reaction" as possible "variables" which could lead to the development of TM. *Id.* at 43. However, these "variables" described by Dr. Höke are also well-established, independent causes for the development of TM without vaccination. His opinion that one of these events need be present for his theory to work calls into question the role the vaccine would actually play in the development of TM in a patient.

Dr. Höke conceded that the "pathogenic mechanism" in his theory is "unknown." Pet'r Ex. 28 at 5. In his report, he equivocated by stating that he believed the process to be "an autoimmune phenomenon related to [a] molecular mimicry hypothesis." *Id.* (citing Pet'r Ex. 33). It is unclear what Dr. Höke means by "related to," but the study that he cites makes clear that there is a "more established link between molecular mimicry and … [GBS]." Pet'r Ex. 37 at 10. The authors of the study are careful to note that "very little is known definitively about the inciting cause of inflammation in the CNS of patients with TM, [and] nothing is currently understood about the mechanisms of tissue injury in this inflammatory disease." *Id.*

Had Petitioner's theory ended there, despite a lack of specificity with respect to the development of TM in vaccinated patients, Petitioner's theory may have been sufficiently plausible under *Althen* prong one. However, Petitioner's expert presented additional evidence to support his

theory which must also be considered to determine its plausibility.[48] This additional information undermined the theory and convoluted Petitioner's position so that it is not, by the preponderance of the evidence, based on a "sound and reliable medical or scientific explanation." *Knudsen*, 35 F.3d at 548.

Dr. Höke testified that his theory is only applicable "in the appropriate environment" wherein some patients develop an antibody response to the vaccine and "those antibodies can get access to the spinal cord and cause [TM]." Tr. 32. Dr. Höke conceded that his theory does not provide an explanation for why all vaccinated persons do not develop TM. He noted only that "there is probably a secondary event that triggers the access of the antibodies to the central nervous system." *Id.* at 36. It is unclear if this secondary event could also be one of the "variables" that affects the significance of the epidemiological studies he discussed. Dr. Höke's examples of a secondary event include "a trauma" or a "genetic makeup" that results in a blood-brain barrier that is "more leaky." *Id.* at 46-47. Dr. Höke did not explain how either of the aforementioned secondary events combine with a vaccination to cause demyelinating disease. This secondary event is not supported by any literature presented by Dr. Höke, and seems to be a catch-all that cannot be disputed or reasoned. In essence, Dr. Höke touts an unspecified, possibly inapplicable mechanism, coupled with an unknown, widely variable and potentially unrelated secondary event. That theory connects Petitioner's case with the existing literature only by the *ipse dixit* of the expert, and it therefore does not meet the preponderant standard. *See Cedillo v. Sec'y of Health & Human Servs.*, 617 F.3d 1328, 1339 (Fed. Cir. 2010) ("A court may conclude that there is simply too great an analytical gap between the data and the opinion proffered.") (quoting *Gen. Elec. Co. v. Joiner*, 522 U.S. 136, 146 (1997)).

C. *Althen* Prong Two

In successful claims, a Petitioner's symptoms can serve to specifically illustrate and reinforce the mechanism that is asserted pursuant to prong one. In Petitioner's case, Dr. Höke applied his causation theory to Petitioner by noting her prior healthy history, confirmed diagnosis of TM, age, and gender. There was no testimony that relied on Petitioner's medical history to explain how or why she, in particular, developed TM following vaccination. Dr. Höke did not point to anything in the record that suggested that Petitioner suffered from an autoimmune and/or inflammatory process. He did not identify Petitioner's necessary "secondary insult" that "makes [her] blood-brain barrier more leaky." *Id.* at 46-47. Petitioner provided no medical tests of testimony to explain why or how the alleged process occurred following Petitioner's third vaccination. Furthermore, Dr. Höke's assertion that the risk for cross-reactivity remains "as long as there's elevated antibody levels in the blood" was weakened under cross-examination. When questioned about a recommendation for "what the peak [time frame] would look like," Dr. Höke

[48] Even though it is well understood that a claimant need not establish a specific biological mechanism in order to meet his burden of proof with respect to the first *Althen* prong, *Althen*, 418 F.3d at 1280, where a claimant offers such evidence and makes it a centerpiece of her causation theory (especially in the absence of other kinds of evidence linking the relevant vaccine to the claimed injury), it is appropriate for the special master to weigh the evidence offered and determine if the claimant has successfully met her self-determined evidentiary goal. *See W.C.*, 704 F.3d at 1360-61.

took his point to an illogical conclusion and noted that "up to three years you have increased risk." *Id.* at 64-65. Dr. Höke's opinion that molecular mimicry is plausible three years following vaccination is not persuasive absent some sort of immunodeficiency or suppressed immune system.

Often, an expert will use the temporal relationship between the vaccination and the onset of injuries to explain how an autoimmune response developed into molecular mimicry in a particular case. Petitioners usually rely on the timeline used for GBS table cases as a baseline. Here, Dr. Höke spent a good deal of time explaining why literature that discussed plausible timelines for an autoimmune injury post-vaccination included "artificial cutoff[s]." Tr. 61-62. Dr. Höke also made it clear that epidemiological studies focus on a "standard period" of time between vaccination and onset with little regard to outliers. *Id.* at 37. He then discussed the temporal relationship in Petitioner's case and noted that it is "luck" that determines onset. *Id*. at 65-66. Because there can be "very similar levels of antibodies in [a petitioner's] blood at six weeks, eight weeks or ten weeks," he explained, the increase of antibodies in the blood is the determining factor and it "take[s] some time" for "significant demyelination to result." *Id.* at 42. Attributing the onset of her symptoms to "luck" does not persuasively explain how or why TM occurred in Petitioner's case.

It is not in dispute that Petitioner suffered from TM after she received a series of Hep B vaccinations. However, that chronology of events alone does not provide persuasive evidence under the preponderant standard of causation. Furthermore, Petitioner's own expert admitted that Petitioner is "the appropriate gender and age group," and that Petitioner's age group and gender "put[] her at high risk" for TM. Tr. 38, 44-45. Dr. Höke opined that Petitioner had an "aberrant response" to the Hep B vaccine, which he "suspect[s] [was due to] a combination of [Petitioner's] genetic makeup or other risk factors." *Id.* at 32. However, Dr. Höke did not identify anything about Petitioner's genetic makeup which would make her more susceptible to an "aberrant response" following the vaccine. He likewise did not identify a secondary insult or injury, if any, that Petitioner may have sustained which would support the application of his theory to her case. In fact, Dr. Höke conceded that, if Petitioner had not received the Hep B vaccine, he would characterize her TM as idiopathic. *Id.* at 61. Similarly, Dr. Vartanian testified that Petitioner's TM was idiopathic. *Id.* at 92. Without additional support explaining how or why TM occurred in Petitioner's case, Dr. Höke's opinion appears to be based largely on assumption. Therefore, Petitioner has not established by a preponderance of the evidence that the development of her TM was caused by vaccination as opposed to an idiopathic etiology.

D. *Althen* Prong Three

It is difficult to ascertain whether there was an appropriate temporal relationship between Petitioner's vaccine and the development of her TM based on Dr. Höke's opinion, because he did not clearly define the applicable onset window. Dr. Höke made a distinction between the use of a "cutoff" for "policy purposes" and the application of an "artificial cutoff" to an individual patient. *Id.* at 62, 65. He stated that there are always people that will fall outside of one standard deviation of a cutoff, especially in the context of rare conditions such as TM. Dr. Höke cited the Siegrist article to point out that the immune response to an antigen exposure can result in elevated antibody titers for over six months. Resp't Ex. I at 9. Dr. Höke went on to explain that elevated antibody

levels could result in the development of an autoimmune injury at any time following antigen exposure, and consequently, his theory is not based on a specific timeframe. Dr. Höke's conclusion that the temporal relationship between vaccination and the onset of symptoms is not probative of whether a vaccine-induced injury has occurred appears to be an attempt to explain the 60+ days that lapsed between Petitioner's vaccination and symptoms onset. Instead, it undercuts the persuasiveness of his entire theory. Dr. Höke's suggestion that there may be no time frame at all, when taken to its logical conclusion, presents the possibility raised by Dr. Vartanian that "if we go beyond that rational limit [for timing], then 100 percent of anything that happens to anyone who gets vaccinated will always be legitimate." Tr. 90.

In contrast to Dr. Höke's indefinite timeline, Dr. Vartanian explained that "if [someone is] susceptible to autoimmunity following an immunization, [the question is] not what [that person's] . . . minimal titer requirement is at some distant time point." Tr. 121. Instead, the timeline is driven by "the kinetics of [what happens] after immunization, when [the person first] achieve[s] that . . . minimally[-]required titer, because at that point is when symptoms occur." *Id.* He explained that a person "can have a super high titer and then drop to one-fiftieth . . . or one-tenth of that titer." *Id.* at 121-22. While those lower levels "might still be sufficient," in that they may remain above the person's minimum-susceptibility titer level, the person would have "had it [that titer amount] earlier," before the titer peaked and dropped off. *Id.* at 122. Thus, Dr. Vartanian explained that an autoimmune response mediated by molecular mimicry, if it is going to occur, will occur at "right around" peak concentration, at the point where the minimally-required titer level is first achieved. *Id.* He explained that any incident of autoimmunity at sixty days post-vaccination is "an outlier," and he "imagine[s] that [the 60-day cutoff] came to be to make sure that we were capturing beyond -- beyond question most -- the majority of cases." *Id.* at 130.

Dr. Vartanian went further and also explained Petitioner's misplaced reliance on the bell shape of the animal model graph that he had drawn earlier in his testimony. Tr. 123; Resp't Ex. K (bottom graph). Noting that care must be taken when extrapolating from animal models, Dr. Vartanian explained that the graph he drew was a measure of the severity of an immune response and not a graph representing the "frequency of disease onset." *Id.* at 124. He explained that the animals would "hav[e] their onset all at approximately the same time," but then they would continue to have the disease." *Id.* Dr. Vartanian stated that "the onset isn't variable. The onset is really reliable." *Id.* at 124. Thus, it is not that, as Petitioner's counsel suggested, the onset of disease occurs in "some [people] a bit earlier and some [people] a bit later" after peak immune response. *Id.* at 123. Instead, it is the severity of the resulting disease that follows the bell-shaped curve. *Id.* at 124. He emphasized that it is "very, very reliable" that onset of disease will cluster at or near peak. *Id.*

Dr. Höke did not offer a rebuttal to Dr. Vartanian's explanation of peak immune response and disease onset, which is consistent with other molecular mimicry-based causation theories previously asserted in the Program with successful results. Ultimately, the time lapse between the vaccination and the onset is significant, because from what is known about the human immune system, a response to a particular antigen will occur within a fairly consistent time frame following exposure. Accepting Dr. Höke's theory would require a finding that certain symptoms occurring at any time after vaccination can be connected back to the vaccination. This would essentially "render[] *Althen*'s third prong a nullity[, where] any conceivable timing could qualify as an

appropriate temporal relationship." *Hennessey v. Sec'y of Health & Human Servs.*, 91 Fed. Cl. 126, 141 (2010).

Dr. Höke and Dr. Vartanian agree that Petitioner's symptoms began more than 60 days following vaccination. Using a preponderant standard, that time frame is too long to be consistent with the molecular theory proposed by Dr. Höke, his opinion on onset timing notwithstanding.

VI. Conclusion

There is no dispute that Petitioner has suffered greatly as a result of the severe and swift onset of her TM. She and her family have endured numerous trials, and there will certainly be additional challenges as they continue to adjust to a new way of life. Her claim was brought in good faith, and her strength in recounting these difficult years is to be commended. However, despite a deep sympathy and empathy for what Petitioner has been through, this decision must not take into account any personal feelings or emotions that these cases often evoke. Instead, it must reflect a thorough analysis of the evidence and a thoughtful balance against the applicable legal standards based upon probative weight and persuasiveness. Petitioner has not established by a preponderance of the evidence that her Hep B vaccination caused her TM. Therefore, I must **DENY** entitlement in this case.

In the absence of a timely-filed motion for review filed pursuant to Vaccine Rule 23, **the Clerk of the Court is directed to ENTER JUDGMENT** consistent with this decision.

IT IS SO ORDERED.

s/Herbrina D. Sanders
Herbrina D. Sanders
Special Master